

Neonatal jaundice

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Luke A Jardine and Paul Woodgate

ABSTRACT

INTRODUCTION: About 50% of term and 80% of preterm babies develop jaundice, which usually appears 2 to 4 days after birth, and resolves spontaneously after 1 to 2 weeks. Jaundice is caused by bilirubin deposition in the skin. Most jaundice in newborn infants is a result of increased red cell breakdown and decreased bilirubin excretion. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for unconjugated hyperbilirubinaemia in term and preterm infants? We searched Medline, Embase, The Cochrane Library, and other important databases up to February 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 42 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: albumin infusion, exchange transfusion, home phototherapy, immunoglobulin, hospital phototherapy, and tin-mesoporphyrin.

QUESTIONS

What are the effects of treatments for unconjugated hyperbilirubinaemia in term and preterm infants? 3

INTERVENTIONS

TREATMENTS

Beneficial

Hospital phototherapy 3
Immunoglobulin (in high-risk infants with haemolytic hyperbilirubinaemia) **New** 20

Likely to be beneficial

Exchange transfusion* 18

Unknown effectiveness

Albumin infusion 19
Home versus hospital phototherapy 19
Tin-mesoporphyrin 19

Footnote

*Although we found no RCTs comparing exchange transfusion with no active treatment, there is general consensus that exchange transfusion is effective at reducing serum bilirubin levels.

Key points

- About 50% of term and 80% of preterm babies develop jaundice, which usually appears 2 to 4 days after birth, and resolves spontaneously after 1 to 2 weeks.
Jaundice is caused by bilirubin deposition in the skin. Most jaundice in newborn infants is a result of increased red cell breakdown and decreased bilirubin excretion.
Breastfeeding, haemolysis, and some metabolic and genetic disorders also increase the risk of jaundice.
Unconjugated bilirubin can be neurotoxic, causing an acute or chronic encephalopathy that may result in cerebral palsy, hearing loss, and seizures.
- Phototherapy** provided by conventional or fiberoptic lights in hospital reduces neonatal jaundice compared with no treatment (as assessed by serum bilirubin levels).
Low threshold compared with high threshold phototherapy reduces neurodevelopmental impairment and hearing loss and reduces serum bilirubin on day 5 in extremely low birth weight infants. However, it increases the duration of phototherapy, and there is no effect on mortality or the rate of exchange transfusion.
Close phototherapy compared with distant light-source phototherapy reduces the duration of phototherapy in infants with hyperbilirubinaemia.
- We don't know whether **home phototherapy** is more or less effective than hospital phototherapy as we found no studies comparing the two treatments.
- There is consensus that **exchange transfusion** reduces serum bilirubin levels and prevents neurodevelopmental sequelae, although we found no studies to confirm this.
Exchange transfusion has an estimated mortality of 3 to 4 per 1000 exchanged infants, and 5% to 10% permanent sequelae in survivors.
- We don't know whether **albumin infusion** is beneficial.
- Tin-mesoporphyrin** is not currently licensed for routine clinical use in the UK or US, and further long-term studies are warranted to confirm its place in clinical practice.

- However, tin-mesoporphyrin reduced the need for phototherapy (as assessed by serum bilirubin levels) when given either to preterm infants on the first day, or to jaundiced term or near-term infants within the first few days of life.
- Intravenous **immunoglobulin** reduces the need for exchange transfusion in high-risk infants with haemolytic hyperbilirubinaemia, as well as reduces serum bilirubin levels, the requirement for phototherapy, and the length of hospital stay.

Benefits of **immunoglobulin** were observed when used either alone or in conjunction with phototherapy. No adverse effects were reported. However, we don't know whether immunoglobulin prevents neurodevelopmental sequelae.

DEFINITION	Neonatal jaundice refers to the yellow coloration of the skin and sclera of newborn babies that results from hyperbilirubinaemia.
INCIDENCE/ PREVALENCE	Jaundice is the most common condition requiring medical attention in newborn babies. About 50% of term and 80% of preterm babies develop jaundice in the first week of life. ^[1] Jaundice is also a common cause of re-admission to hospital after early discharge of newborn babies. ^[2] Jaundice usually appears 2 to 4 days after birth and disappears 1 to 2 weeks later, usually without the need for treatment.
AETIOLOGY/ RISK FACTORS	Jaundice occurs when there is accumulation of bilirubin in the skin and mucous membranes. In most infants with jaundice, there is no underlying disease, and the jaundice is termed physiological. Physiological jaundice typically presents on the second or third day of life, and results from the increased production of bilirubin (owing to increased circulating red cell mass and a shortened red cell lifespan) and the decreased excretion of bilirubin (owing to low concentrations of the hepatocyte binding protein, low activity of glucuronosyl transferase, and increased enterohepatic circulation) that normally occur in newborn babies. Breastfed infants are more likely to develop jaundice within the first week of life; this is thought to be an exacerbated physiological jaundice caused by a lower calorific intake and increased enterohepatic circulation of bilirubin. Prolonged unconjugated jaundice, persisting beyond the second week, is also seen in breastfed infants. The mechanism for this later "breast milk jaundice syndrome" is still not completely understood. Non-physiological causes include blood group incompatibility (rhesis or ABO problems), other causes of haemolysis, sepsis, bruising, and metabolic disorders. Gilbert's and Crigler–Najjar syndromes are rare causes of neonatal jaundice.
	Jaundice is usually seen first in the face, and progresses caudally to the trunk and extremities. However, visual estimation of the bilirubin levels can lead to errors, and a low threshold should exist for measuring serum bilirubin. There are devices that measure transcutaneous bilirubin, but these are generally for screening purposes. ^[3]
PROGNOSIS	In the newborn baby, unconjugated bilirubin can penetrate the blood–brain barrier and is potentially neurotoxic. Acute bilirubin encephalopathy consists of initial lethargy and hypotonia, followed by hypertonia (retrocollis and opisthotonus), irritability, apnoea, and seizures. Kernicterus refers to the yellow staining of the deep nuclei of the brain — namely, the basal ganglia (globus pallidus); however, the term is also used to describe the chronic form of bilirubin encephalopathy, which includes symptoms such as athetoid cerebral palsy, hearing loss, failure of upward gaze, and dental enamel dysplasia. The exact level of bilirubin that is neurotoxic is unclear, and kernicterus at autopsy has been reported in infants in the absence of markedly elevated levels of bilirubin. ^[4] Reports suggest a resurgence of kernicterus in countries in which this complication had virtually disappeared. ^[5] This has been attributed mainly to early discharge of newborns from hospital.
AIMS OF INTERVENTION	To prevent the development of bilirubin-associated neurodevelopmental sequelae; to reduce serum bilirubin levels, with minimal adverse effects.
OUTCOMES	Mortality; neurological/neurodevelopmental (including neurodevelopmental delay, incidence of kernicterus and other neurodevelopmental sequelae, hearing loss, blindness); need for exchange transfusion; duration of treatment (including duration of phototherapy, need for re-treatment with phototherapy, need for phototherapy due to treatment failure); serum bilirubin levels; adverse effects of treatments (including effects on parent–infant bonding). Wherever possible, we have reported on our prespecified clinical outcomes of interest such as neurodevelopmental delay or sequelae. However, many studies did not report on clinical outcomes, but on biochemical measures such as serum bilirubin levels. Hence, we have also reported these non-clinical outcomes.
METHODS	<i>Clinical Evidence</i> search and appraisal February 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2010, Embase 1980 to February 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 1 (1966 to date of issue) and The Cochrane Database of Systematic Reviews 2010 online February 2010 release.

An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. Considering the population and nature of the interventions involved we also included studies described as "open", "open label", or "not blinded". We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION	What are the effects of treatments for unconjugated hyperbilirubinaemia in term and preterm infants?
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OPTION	HOSPITAL PHOTOTHERAPY
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Mortality

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, serum bilirubin [SBR] expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) and high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) seem equally effective at improving mortality before day 15, mortality before discharge, and mortality or the composite outcome of mortality and neurodevelopmental impairment at 18 to 22 months in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality ([moderate-quality evidence](#)).

Neurological/neurodevelopmental

Conventional phototherapy compared with no treatment We don't know whether conventional phototherapy is more effective than no treatment at reducing cerebral palsy or other motor abnormalities (clumsiness, hypotonia, abnormal movement) at 1 or 6 years in infants with hyperbilirubinaemia as we found insufficient evidence from one RCT. The study did not use very intensive phototherapy ([low-quality evidence](#)).

Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR >150 micromol/L) at reducing the proportion of infants with either cerebral palsy, with the composite outcome of cerebral palsy or death, or with an abnormal developmental index score at 18 months, in infants of birth weight <1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly ([very low-quality evidence](#)).

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems more effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at reducing the proportion of infants with neurodevelopmental impairment, profound impairment, and severe hearing loss at 18 to 22 months in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality, but we don't know about cerebral palsy or blindness ([moderate-quality evidence](#)).

Need for exchange transfusion

Conventional phototherapy compared with no treatment Conventional phototherapy may be more effective than no treatment at reducing exchange transfusion in infants with established hyperbilirubinaemia and birth weight of 2000–2499 g, but we don't know about in infants of 2500 g or over. Subgroup analysis suggests that conventional

phototherapy may be more effective than no treatment at reducing exchange transfusion in infants with established hyperbilirubinaemia with non-haemolytic jaundice, but we don't know about in infants with haemolytic jaundice. The study did not use very intensive phototherapy, which may explain the lack of effect of phototherapy in some subgroups (low-quality evidence).

Conventional phototherapy compared with fibreoptic phototherapy We don't know whether conventional phototherapy and fibreoptic phototherapy differ in effectiveness at reducing the proportion of infants who require exchange transfusion (very low-quality evidence).

Double compared with single phototherapy We don't know whether fibreoptic plus conventional phototherapy is more effective than conventional phototherapy alone at reducing the rate of exchange transfusion as we found insufficient evidence from one small RCT (low-quality evidence).

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) and high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) seem equally effective at preventing the need for exchange transfusions in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality (moderate-quality evidence).

Phototherapy compared with immunoglobulin Phototherapy (continuous or intermittent blue light exposure in analysis) may be less effective than intravenous immunoglobulin for 3 consecutive days at reducing the rate of exchange transfusion (further details not reported) in neonates diagnosed with ABO haemolytic disease of the newborn (ABO-HDN), mother with blood type O, anti-A/B valence >1:128, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia (very low-quality evidence).

Duration of treatment

Fibreoptic phototherapy compared with no treatment We don't know whether fibreoptic phototherapy is more effective than no treatment at reducing the proportion of infants who require conventional phototherapy in term infants with haemolysis excluded (low-quality evidence).

Conventional phototherapy compared with fibreoptic phototherapy Conventional phototherapy may be more effective than fibreoptic phototherapy at reducing the duration of phototherapy treatment and the use of additional phototherapy treatment in term and preterm infants analysed as a group, but we don't know about duration of phototherapy or additional phototherapy in preterm infants alone (very low-quality evidence).

Double compared with single phototherapy Double conventional phototherapy (using daylight fluorescent lamps) may be more effective than single conventional phototherapy at reducing the duration of treatment in term infants of birth weight 2500 g or above with haemolysis included. Conventional phototherapy plus fibreoptic Wallaby phototherapy may be more effective than Wallaby, BiliBlanket, or conventional phototherapy alone at reducing mean duration of treatment in preterm infants of <31 weeks' gestation with haemolytic jaundice excluded. We don't know whether fibreoptic plus conventional phototherapy is more effective than single conventional phototherapy in reducing the need for additional phototherapy or repeat phototherapy for rebound jaundice in term and preterm infants. We don't know whether double fibreoptic phototherapy (infants wrapped in 2 BiliBlankets) is more effective than single conventional therapy at reducing duration of treatment or use of repeat phototherapy in term infants with haemolysis excluded (very low-quality evidence).

Intermittent phototherapy compared with continuous phototherapy We don't know whether intermittent equal duration phototherapy (4 hours on, 4 hours off), intermittent short duration phototherapy (1 hour on, 3 hours off), and continuous phototherapy differ in effectiveness at reducing duration of phototherapy treatment in term infants who are 2500 g or above with physiological jaundice (low-quality evidence).

Close phototherapy compared with distant light-source phototherapy Close light-source conventional phototherapy from a distance of 20 cm above the neonate seems more effective than more distant light-source phototherapy at 40 cm above the neonate at reducing mean duration of treatment in infants with hyperbilirubinaemia not severe enough to require exchange transfusion and with absence of congenital metabolic disorders (moderate-quality evidence).

Increased skin exposure compared with standard skin exposure phototherapy We don't know whether conventional phototherapy in partially clothed infants (disposable nappy only) and conventional phototherapy in naked infants differ in effectiveness at reducing the proportion of infants still requiring phototherapy at 24 to 48 hours and 48 to 72 hours in preterm infants of 1500 g or more and 36 weeks' gestation or less with non-haemolytic hyperbilirubinaemia with total serum bilirubin in the range for phototherapy (low-quality evidence).

Fluorescent compared with blue fluorescent lamps We don't know whether daylight fluorescent lamps, standard blue fluorescent lamps, and blue fluorescent lamps with a narrow spectral emission differ in effectiveness at improving the proportion of infants who discontinue phototherapy after 1 to 3 days in infants with hyperbilirubinaemia in the first 72 hours of life (non-haemolytic) as the RCT did not test the significance of differences between groups (low-quality evidence).

Blue fluorescent compared with green fluorescent lamps Blue fluorescent lamps and green fluorescent lamps seem equally effective at reducing the duration of phototherapy in term and preterm infants with non-haemolytic jaundice (moderate-quality evidence).

Blue-green fluorescent compared with blue fluorescent lamps Blue-green fluorescent light may be more effective than blue fluorescent light at reducing the proportion of infants requiring phototherapy after 24 hours in healthy low birth weight infants with hyperbilirubinaemia in the first 4 days of life, but we don't know whether 6 focused arrays of blue-green LED phototherapy is more effective than 6 focused arrays of blue LED phototherapy at increasing the mean rate of serum bilirubin decline in jaundiced but otherwise healthy term infants (very low-quality evidence).

Blue LED compared with conventional quartz-halogen We don't know whether blue LED and conventional phototherapy (using halogen-quartz bulbs) differ in effectiveness at reducing the mean number of hours spent under phototherapy as we found insufficient evidence (low-quality evidence).

Blue-green LED compared with conventional quartz-halogen We don't know whether 6 focused arrays of blue-green LED phototherapy and conventional phototherapy consisting of three halogen-quartz bulbs differ in effectiveness at reducing the mean number of hours of phototherapy in jaundiced but otherwise healthy term infants (low-quality evidence).

Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR >150 micromol/L) at reducing the mean number of hours of phototherapy in infants of birth weight <1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly (low-quality evidence).

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems less effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at reducing the duration of phototherapy in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality. We don't know whether commencing phototherapy once SBR is >13 mg/dL, commencing phototherapy once SBR is 10 mg/dL or above and treating for 12 hours, and commencing phototherapy once SBR is 10 mg/dL or above and treating for 24 hours differ in effectiveness at reducing the proportion of infants who receive phototherapy at <72 hours or >72 hours in infants of birth weight <2500 g (moderate-quality evidence).

Compact fluorescent light phototherapy compared with standard length tube light phototherapy We don't know whether compact fluorescent light phototherapy is more effective than standard length tube light phototherapy at reducing the total duration of treatment required in infants above 34 weeks' gestation with haemolytic jaundice excluded (low-quality evidence).

Phototherapy compared with immunoglobulin Phototherapy (continuous or intermittent blue light exposure in analysis) may be less effective than intravenous immunoglobulin for 3 consecutive days at reducing the duration of phototherapy in neonates diagnosed with ABO-HDN, mother with blood type O, anti-A/B valence >1:128, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia (low-quality evidence).

Serum bilirubin level

Conventional phototherapy compared with no treatment Conventional phototherapy may be more effective than no treatment at reducing the proportion of infants with maximal serum bilirubin levels and may be more effective at reducing mean serum bilirubin levels in infants with hyperbilirubinaemia (low-quality evidence).

Continuous phototherapy compared with no treatment We don't know whether continuous phototherapy is more effective than no treatment at reducing the proportion of infants with serum bilirubin levels >12 mg/dL and >15 mg/dL in preterm infants of birth weight 1250–2000 g who were Coombs' negative with no haemolytic anaemia as the RCT did not test differences between groups. However, absolute rates were lower in the continuous phototherapy group (low-quality evidence).

Intermittent phototherapy compared with no treatment We don't know whether intermittent phototherapy (12 hours on, 12 hours off) is more effective than no treatment at reducing the proportion of infants with serum bilirubin levels >12 mg/dL and >15 mg/dL in preterm infants of birth weight 1250–2000 g who were Coombs' negative with no

haemolytic anaemia as the RCT did not test differences between groups. However, absolute rates were lower in the intermittent phototherapy group (low-quality evidence).

Fibreoptic phototherapy compared with no treatment Fibreoptic phototherapy may be more effective than no treatment at increasing the percentage change in serum bilirubin per hour and the percentage change after 24 hours of treatment in term infants with haemolysis excluded (low-quality evidence).

Conventional phototherapy compared with fibreoptic phototherapy Conventional phototherapy may be more effective than fibreoptic phototherapy at increasing the percentage change in serum bilirubin at 24 hours and 48 hours in term and preterm infants analysed as a group, but we don't know about percentage change in serum bilirubin at 24 hours in preterm infants alone (very low-quality evidence).

Double phototherapy compared with single phototherapy Double conventional phototherapy (using daylight fluorescent lamps) may be more effective than single conventional phototherapy at increasing the rate of reduction of serum bilirubin in term infants of birth weight 2500 g or above with haemolysis included. Conventional phototherapy plus fibreoptic Wallaby phototherapy may be more effective than Wallaby, BiliBlanket, or conventional phototherapy alone at reducing the increase in bilirubin levels over the first 24 hours in preterm infants of <31 weeks' gestation with haemolytic jaundice excluded. We don't know whether fibreoptic plus conventional phototherapy is more effective than single conventional phototherapy at improving the percentage change in serum bilirubin levels after 24 or 48 hours in term and preterm infants. We don't know whether double fibreoptic phototherapy (infants wrapped in 2 Bili-Blankets) is more effective than single conventional therapy at improving the percentage change in serum bilirubin per hour or per day in term infants with haemolysis excluded. Double surface phototherapy may be more effective than single surface phototherapy at increasing the total decline in serum bilirubin levels after 48 hours in term infants of 2500 g or above with non-haemolytic hyperbilirubinaemia who were exclusively breastfed, but we don't know whether it is more effective at 24 to 48 hours (very low-quality evidence).

Triple phototherapy compared with double phototherapy We don't know whether triple phototherapy (2 single fluorescent lamps 25 cm above bed plus third fluorescent lamp 35 cm from bed) is more effective than double phototherapy (2 single fluorescent lamps 25 cm above bed) at improving mean bilirubin levels at 8, 16, or 24 hours in infants of 2500 g or more and of 37 weeks' gestation or above with non-haemolytic jaundice (low-quality evidence).

Intermittent phototherapy compared with continuous phototherapy We don't know whether intermittent phototherapy (1 hour on, 1 hour off) is more effective than continuous phototherapy (2 hours on, 30 minutes off) at improving mean serum bilirubin levels at 12, 24, 36, and 48 hours in infants above 2000 g with hyperbilirubinaemia not exceeding the range for exchange transfusion nor requiring high intensity phototherapy. We don't know whether continuous phototherapy and intermittent phototherapy (12 hours on, 12 hours off) differ in effectiveness at reducing the proportion of infants with serum bilirubin levels of >12 mg/dL or >15 mg/dL in preterm infants with birth weight 1250–2000 g who were Coombs' negative with no haemolytic anaemia as the trial did not test the significance of differences between groups. We don't know whether intermittent equal duration phototherapy (4 hours on, 4 hours off), intermittent short duration phototherapy (1 hour on, 3 hours off), and continuous phototherapy differ in effectiveness at slowing the rate of increase in bilirubin levels or improving the rate of decrease of bilirubin levels in term infants of 2500 g or above with physiological jaundice (low-quality evidence).

Increased skin exposure compared with standard skin exposure phototherapy We don't know whether conventional phototherapy in partially clothed infants (disposable nappy only) and conventional phototherapy in naked infants differ in effectiveness at improving the mean percentage decline in serum bilirubin levels or the absolute change in mean serum bilirubin levels in preterm infants of 1500 g or more and of 36 weeks' gestation or less with non-haemolytic hyperbilirubinaemia with total serum bilirubin in the range for phototherapy (low-quality evidence).

Fluorescent lamps compared with halide lamps We don't know whether fluorescent and halide lamps differ in effectiveness at improving serum bilirubin levels at 24 hours in infants with non-haemolytic hyperbilirubinaemia of 40 hours of age or more (low-quality evidence).

Fluorescent compared with blue fluorescent lamps We don't know whether daylight fluorescent lamps, standard blue fluorescent lamps, and blue fluorescent lamps with a narrow spectral emission differ in effectiveness at improving the mean decrease of serum bilirubin levels at 1 to 3 days in infants with hyperbilirubinaemia in the first 72 hours of life (non-haemolytic) as the RCT did not test the significance of differences between groups (low-quality evidence).

Blue fluorescent compared with green fluorescent lamps We don't know whether blue fluorescent lamps and green fluorescent lamps differ in effectiveness at increasing the rate of fall of serum bilirubin in term and preterm infants with non-haemolytic jaundice or in low birth weight infants with non-haemolytic jaundice stratified by initial serum bilirubin levels (21–16.1 mg/dL; 16–12.1 mg/dL; 12–9.0 mg/dL) (low-quality evidence).

Blue-green fluorescent compared with blue fluorescent lamps We don't know whether blue-green fluorescent and blue fluorescent phototherapy differ in effectiveness at improving serum bilirubin levels. There were conflicting results between trials depending on the population studied, the exact intervention used, and the analysis undertaken (very low-quality evidence).

Blue LED compared with conventional quartz-halogen We don't know whether blue LED and conventional phototherapy (using halogen-quartz bulbs) differ in effectiveness at improving the rate of serum bilirubin decline as we found insufficient evidence (low-quality evidence).

Blue LED compared with blue fluorescent lamps We don't know whether blue LED (overhead neoBLUE LED plus either BiliBlanket or Wallaby system underneath) and phototherapy with blue fluorescent lights (8 overhead blue fluorescent lights plus either BiliBlanket or Wallaby system underneath) differ in effectiveness at improving the decline of serum bilirubin levels in infants of 35 weeks' gestation or more (very low-quality evidence).

Blue-green LED compared with conventional quartz-halogen We don't know whether 6 focused arrays of blue-green LED phototherapy and conventional phototherapy consisting of three halogen-quartz bulbs differ in effectiveness at improving the mean rate of serum bilirubin decline in jaundiced but otherwise healthy term infants (low-quality evidence).

Prophylactic phototherapy compared with threshold phototherapy We don't know whether prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) is more effective than threshold phototherapy (commencement once SBR >150 micromol/L) at reducing peak unconjugated serum bilirubin levels in infants of birth weight <1500 g within 12 hours of birth without isoimmunisation or major life-threatening anomaly. Subgroup analysis suggests that prophylactic phototherapy may be more effective than threshold phototherapy at reducing peak unconjugated serum bilirubin levels in infants with a birth weight <1000 g, but not in infants with a birth weight of 1000–1499 g (low-quality evidence).

Low threshold compared with high threshold phototherapy Low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L and recommencement of phototherapy if SBR >85 micromol/L in first 7 days of life or SBR >137 micromol/L from day 7–14 of life) seems more effective than high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR >137 micromol/L in first 7 days and SBR >171 micromol/L from day 7–14 of life) at decreasing the level of serum bilirubin at day 5 in extremely low birth weight infants 12 to 36 hours old with non-severe haemolytic disease and absence of major congenital abnormality (moderate-quality evidence).

Compact fluorescent light phototherapy compared with standard length tube light phototherapy Compact fluorescent light phototherapy may be more effective than standard length tube light phototherapy at reducing the mean total serum bilirubin over 12 hours in infants above 34 weeks' gestation with haemolytic jaundice excluded (low-quality evidence).

Phototherapy compared with immunoglobulin Phototherapy (continuous or intermittent blue light exposure in analysis) may be less effective than intravenous immunoglobulin for 3 consecutive days at lowering serum bilirubin levels and increasing the drop in serum bilirubin levels at 3 days in neonates diagnosed with ABO-HDN, mother with blood type O, anti-A/B valence >1:128, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia (low-quality evidence).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits:

Conventional phototherapy versus no treatment:

We found one systematic review (search date 2001),^[3] which included two RCTs,^[6] ^[7] although their results were not combined statistically. Neither of these studies assessed the primary outcomes of this review.

The largest RCT identified by the review compared conventional phototherapy using daylight fluorescent lamps versus no treatment in three birth weight groups (<2000 g, 2000–2499 g, and 2500 g and over).^[6] Exchange transfusion was given at predetermined serum bilirubin levels in each group. The RCT examined prevention of hyperbilirubinaemia in the lowest birth weight group, and treatment of established hyperbilirubinaemia in the remaining two groups. Only the results of treatment of established hyperbilirubinaemia are reported here. The RCT found that in the 2000–2499 g birth weight group (141 infants, serum bilirubin [SBR] 171 micromol/L or more, average 212 micromol/L), phototherapy significantly reduced the proportion of infants with higher maximal serum bilirubin levels compared with no treatment (SBR 257 micromol/L or more: 18.6% with phototherapy v 42.3% with no treatment; $P = 0.002$). For this group, it found that phototherapy significantly decreased the proportion of infants who needed exchange transfusion compared with no treatment (4.3% with phototherapy v 25.4% with no treatment; $P < 0.001$). The RCT found that, in the 2500 g or over birth weight group (276 infants, SBR 222 micromol/L or more, average 267–268 micromol/L), phototherapy significantly reduced mean serum bilirubin levels until 24 hours after stopping treatment compared with no treatment (results presented graphically; P value not reported). The RCT found no significant difference between phototherapy and no treatment in the proportion of infants who needed exchange transfusion (10.0% with phototherapy v 16.9% with no treatment; reported as not significant). In both birth weight groups, subgroup analysis suggested

that, in infants with non-haemolytic jaundice, phototherapy significantly decreased exchange transfusion compared with no treatment (infants 2000–2499 g: 1.9% with phototherapy v 27.5% with no treatment; $P = 0.0002$; infants 2500 g or more: 2.9% with phototherapy v 17.3% with no treatment; $P = 0.05$), but there was no evidence of effectiveness in preventing exchange transfusion in infants with haemolytic jaundice.^[6] A subsequent report of the RCT noted that there were two deaths before hospital discharge (2000–2499 g group: 1 with phototherapy v 1 with no treatment; 2500 g or more group: none).^[8] A further follow-up report of the RCT found no significant difference in cerebral palsy or other motor abnormalities (clumsiness, hypotonia, abnormal movement) after 1 and 6 years in either of the birth weight groups.^[9]

The smaller RCT identified by the review compared the effect of 4 interventions on hyperbilirubinaemia (SBR >291 micromol/L) on 125 term breastfed infants.^[7] The 4 interventions were: continue breastfeeding and observe (25 infants), substitute formula feed (26 infants), continue breastfeeding and administer phototherapy (36 infants), and substitute formula and administer phototherapy (38 infants). Phototherapy resulted in a smaller proportion of infants whose serum bilirubin rose above 342 micromol/L (8.1% of 74 infants receiving phototherapy v 21.6% of 51 infants not receiving phototherapy; RR 0.34, 95% CI 0.15 to 0.95; see comment).

Continuous phototherapy versus no treatment:

We found one RCT comparing continuous phototherapy versus no treatment.^[10]

The three-armed RCT (120 preterm infants, birth weight 1250–2000 g, Coombs' negative, no haemolytic anaemia, no gross congenital anomalies, no severe respiratory distress syndrome) compared continuous phototherapy versus no treatment versus intermittent phototherapy (12 hours on, 12 hours off) for 5 days. We only report the data for continuous phototherapy compared with no treatment here.^[10] The RCT found that a smaller proportion of preterm infants treated with continuous phototherapy had serum bilirubin levels >12 mg/dL and >15 mg/dL (note: 1 mg/dL = 17.1 micromol/L [SI unit]) compared with no treatment (>12 mg/dL: 2/40 [5%] with continuous phototherapy v 14/40 [35%] with no treatment; >15 mg/dL: 0/40 [0%] with continuous phototherapy v 5/40 [13%] with no treatment; P values not reported).^[10]

Intermittent phototherapy versus no treatment:

We found one RCT comparing intermittent phototherapy versus no treatment.^[10]

The three-armed RCT (120 preterm infants, birth weight 1250–2000 g, Coombs' negative, no haemolytic anaemia, no gross congenital anomalies, no severe respiratory distress syndrome) compared continuous phototherapy versus no treatment versus intermittent phototherapy (12 hours on, 12 hours off) for 5 days. We only report the data for intermittent phototherapy compared with no treatment here. The RCT found that a smaller proportion of preterm infants treated with intermittent phototherapy had serum bilirubin levels >12 mg/dL and >15 mg/dL compared with no treatment (>12 mg/dL: 3/40 [8%] with intermittent phototherapy v 14/40 [35%] with no treatment; >15 mg/dL: 1/40 [3%] with intermittent phototherapy v 5/40 [13%] with no treatment; P values not reported).^[10]

Fibreoptic phototherapy versus no treatment:

We found one systematic review (search date 2000; term and preterm infants; randomised and quasi-randomised trials; see comment below).^[11] The review identified one RCT (46 term infants, haemolysis excluded), which compared fibreoptic phototherapy (Wallaby system) versus no treatment. Conventional phototherapy was commenced if the serum bilirubin reached predetermined levels. The review found that, compared with no treatment, fibreoptic phototherapy significantly increased the percentage change in serum bilirubin per hour (WMD -0.44%, 95% CI -0.67% to -0.21%) and the percentage change after 24 hours of treatment (WMD -10.70%, 95% CI -18.14% to -3.26%).^[11] It found that infants in the fibreoptic phototherapy group were less likely to require conventional phototherapy, but this did not reach significance (0/23 [0%] with fibreoptic phototherapy v 3/23 [13%] with no treatment; RR 0.14, 95% CI 0.01 to 2.62).

Conventional versus fibreoptic phototherapy:

We found one systematic review (search date 2000; term and preterm infants; randomised and quasi-randomised trials; see comment below)^[11] and two subsequent RCTs.^{[12] [13]}

The review found that conventional phototherapy significantly increased the percentage change in serum bilirubin after 24 and 48 hours of treatment compared with fibreoptic phototherapy (24 hours: 5 trials, 203 infants; WMD 3.59%, 95% CI 1.27% to 5.92%; 48 hours: 4 trials, 183 infants; WMD 10.79%, 95% CI 8.33% to 13.26%).^[11] It also found that fibreoptic phototherapy significantly increased the use of additional phototherapy compared with conventional phototherapy (8 trials: 52/366 [14%] with fibreoptic v 35/390 [9%] with conventional; RR 1.68, 95% CI 1.18 to 2.38), and also resulted in an increase in duration of phototherapy treatment (6 trials, 562 infants: WMD +13.6

hours, 95% CI +10.1 hours to +17.1 hours). It found no significant difference between fiberoptic and conventional phototherapy in the use of exchange transfusion (3 trials: 4/97 [4%] with fiberoptic v 3/117 [3%] with conventional; RR 1.62, 95% CI 0.38 to 6.93). In a subgroup analysis of preterm babies only, the review found no significant difference between fiberoptic phototherapy and conventional phototherapy in the duration of phototherapy, use of additional phototherapy, percentage change in serum bilirubin after 24 hours of treatment, percentage change in serum bilirubin after 24 hours of treatment, and repeat phototherapy for rebound jaundice (duration of phototherapy: 3 trials, 232 infants; WMD +2.00 hours, 95% CI -3.50 hours to +7.52 hours; use of additional phototherapy: 5 trials; 3/148 [2.0%] with fiberoptic v 3/156 [1.9%] with conventional; RR 1.07, 95% CI 0.27 to 4.27; percentage change in serum bilirubin after 24 hours of treatment: 1 trial, 20 infants; WMD +1.7%, 95% CI -2.65% to +6.05%; repeat phototherapy for rebound jaundice: 3 trials; 10/122 [8%] with fiberoptic v 5/121 [4%] with conventional; RR 2.00, 95% CI 0.71 to 5.63).^[11]

The first subsequent RCT (109 term infants, birth weight 2500 g or more, infants with haemolytic jaundice excluded) found that conventional daylight phototherapy significantly increased the rate of decline of serum bilirubin, and decreased treatment duration compared with fiberoptic phototherapy (bilirubin decline rate: 2.6 ± 1.0 micromol/L/hour with conventional v 1.7 ± 0.9 micromol/L/hour with fiberoptic; $P < 0.05$; duration of phototherapy: 49.4 ± 14.4 hours with conventional v 61 ± 13.1 hours with fiberoptic; $P < 0.05$).^[12]

The second subsequent RCT (140 preterm infants, gestation <31 weeks, infants with haemolytic jaundice excluded) compared single conventional phototherapy, fiberoptic Wallaby phototherapy, fiberoptic BiliBlanket phototherapy, and combined conventional plus fiberoptic Wallaby phototherapy. We only report data on the conventional, fiberoptic Wallaby and fiberoptic BiliBlanket groups here. The RCT found no significant difference in the duration of treatment required for either Wallaby and BiliBlanket fiberoptic phototherapy compared with conventional phototherapy alone (92 hours with Wallaby v 95 hours with BiliBlanket v 90 hours with conventional: reported as not significant; P value not reported).^[13]

Double versus single phototherapy:

We found one systematic review (search date 2000; term and preterm infants; randomised and quasi-randomised trials; see comment below)^[11] and three subsequent RCTs.^{[14] [13] [15]}

The systematic review included one RCT (86 term infants, haemolysis excluded) comparing double fiberoptic phototherapy (infants wrapped in 2 BiliBlankets) versus single conventional phototherapy.^[11] The RCT included in the review found no significant difference between groups in duration of treatment, percentage change in serum bilirubin per hour, percentage change in serum bilirubin per day, and the use of repeat phototherapy for rebound jaundice (duration of treatment: WMD +2.24 hours, 95% CI -10.68 hours to +15.16 hours; percentage change in serum bilirubin per hour: WMD -0.04%, 95% CI -0.17% to +0.09%; percentage change in SBR per day: WMD +2.82%, 95% CI -1.84% to +7.48%; and the use of repeat phototherapy for rebound jaundice: RR 1.05, 95% CI 0.07 to 16.22).^[11] The review also compared double phototherapy using a combination of fiberoptic plus conventional phototherapy versus conventional phototherapy alone. It found no significant difference between fiberoptic plus conventional phototherapy and single conventional phototherapy in exchange transfusion, additional phototherapy, and percentage change in serum bilirubin after 24 or 48 hours, although it noted a trend favouring the fiberoptic plus conventional group (exchange transfusion: 1 trial; 0/19 [0%] with fiberoptic plus conventional v 2/23 [8%] with conventional alone; RR 0.24, 95% CI 0.01 to 4.72; additional phototherapy: 1 trial; 0/90 [0%] with fiberoptic plus conventional v 4/90 [4%] with conventional; RR 0.11, 95% CI 0.01 to 2.02; percentage change in SBR after 24 hours: 1 trial, 26 infants; WMD -3.2%, 95% CI -17.2% to +10.8%; percentage change in SBR after 48 hours: WMD -9.2%, 95% CI -25.02% to +6.62%). It found no significant difference between fiberoptic plus conventional phototherapy and single conventional phototherapy in repeat phototherapy for rebound jaundice (6 trials; 36/232 [16%] with fiberoptic plus conventional v 30/240 [13%] with conventional; RR 1.29, 95% CI 0.85 to 1.95).^[11]

The first subsequent RCT (51 term infants, birth weight 2500 g or more, haemolysis included) compared double conventional phototherapy using daylight fluorescent lamps versus single conventional phototherapy.^[14] It found that double conventional phototherapy reduced serum bilirubin at a significantly higher rate during the first 24 hours compared with single conventional phototherapy (3.8 ± 2.1 micromol/L/hour with double v 2.4 ± 1.7 micromol/L/hour with single; $P = 0.02$). It found a trend for double conventional phototherapy to reduce bilirubin at a higher rate on the second day, but this did not reach significance ($P = 0.06$). It found that double conventional phototherapy significantly reduced duration of treatment compared with single conventional phototherapy (34.9 ± 12.6 hours with double v 43.7 ± 17.5 hours with single; $P = 0.039$). It did not report on kernicterus or other long-term outcomes.

The second subsequent RCT (140 preterm infants, gestation <31 weeks, infants with haemolytic jaundice excluded) compared single conventional phototherapy, fibreoptic Wallaby phototherapy, fibreoptic BiliBlanket phototherapy, and combined conventional plus fibreoptic Wallaby phototherapy.^[13] It found that the combined phototherapy reduced mean duration of treatment required compared with either of the treatments used alone (Wallaby: 92 hours; BiliBlanket: 95 hours; conventional: 90 hours; combined Wallaby and conventional: 75 hours; $P < 0.05$ for combined Wallaby and conventional v either Wallaby or BiliBlanket alone; $P < 0.01$ for combined Wallaby and conventional v conventional alone). It also found that the combination of conventional phototherapy plus Wallaby fibreoptic phototherapy produced a smaller increase in bilirubin levels over the first 24 hours compared with conventional phototherapy alone (16% with conventional plus Wallaby fibreoptic v 27% with conventional alone; $P < 0.01$).^[13]

The third subsequent RCT (60 term infants 37–42 weeks, birth weight 2500 g or more, exclusively breastfed, 1- and 5-minute Apgar scores >6, total SBR 13.0–19.9 mg/dL, with non-haemolytic hyperbilirubinaemia) compared double surface phototherapy (4 deep blue and 2 daylight fluorescent lamps at least 30 cm above the baby plus 4 deep blue fluorescent lamps 25 cm below the baby) with single surface phototherapy (4 deep blue and 2 daylight fluorescent lamps at least 30 cm above the baby).^[15] The RCT found no significant difference in the mean serum bilirubin levels between double surface phototherapy compared with single surface phototherapy at 24 hours (10.3 ± 1.9 mg/dL with double surface phototherapy v 11.3 ± 2.1 mg/dL with single surface phototherapy; $P = 0.05$). However, the RCT found that compared with single surface phototherapy, double surface phototherapy significantly increased levels of decline in serum bilirubin after 24 hours (5.4 ± 2.0 mg/dL with double surface v 3.5 ± 1.7 mg/dL with single surface; $P < 0.001$). The RCT found no significant difference between groups in the total declined serum bilirubin levels between 24 and 48 hours (3.1 ± 1.7 mg/dL with double surface v 3.0 ± 1.8 mg/dL with single surface; $P = 0.9$). The RCT also found that compared with single surface phototherapy, double surface phototherapy significantly increased total decline in serum bilirubin levels after 48 hours (8.4 ± 1.7 mg/dL with double surface v 6.5 ± 2.3 mg/dL with single surface; $P = 0.001$). No exchange transfusions were performed in either group.^[15]

Triple versus double phototherapy:

We found one RCT (40 infants >37 weeks' gestation, >2500 g, with no medical problems and non-haemolytic jaundice) comparing triple phototherapy (2 single fluorescent lamps 25 cm above bed plus third fluorescent lamp 35 cm from bed) with double phototherapy (2 single fluorescent lamps 25 cm above bed).^[16] The RCT found no significant difference between triple and double phototherapy in the length of hospital stay (41.5 ± 17.7 hours with triple v 34.6 ± 16.5 hours with double; $P = 0.211$). The RCT also found no significant difference in mean bilirubin levels between triple and double phototherapy at 8, 16, or 24 hours (8 hours: 14 ± 1.7 mg/dL with triple v 13.7 ± 1.8 mg/dL with double; $P = 0.59$; 16 hours: 12.4 ± 1.7 mg/dL with triple v 12.2 ± 1.7 mg/dL with double; $P = 0.76$; 24 hours: 10.9 ± 1.0 mg/dL with triple v 10.3 ± 2.0 mg/dL with double; $P = 0.37$).^[16]

Intermittent versus continuous phototherapy:

We found three RCTs comparing intermittent versus continuous phototherapy.^{[10] [17] [18]}

The first RCT (114 infants >2000 g, absence of concomitant disease, hyperbilirubinaemia not exceeding the range for exchange transfusion or requiring high intensity phototherapy) compared intermittent phototherapy (phototherapy on for 1 hour then off for 1 hour) versus continuous phototherapy (2 hours on, 30 minutes off).^[17] The RCT found no significant difference between intermittent compared with continuous phototherapy in mean serum bilirubin level at 12, 24, 36, and 48 hours (12 hours: 13.57 ± 2.30 mg/dL with intermittent v 13.73 ± 1.89 mg/dL with continuous; $P = 0.6$; 24 hours: 10.86 ± 2.13 mg/dL with intermittent v 11.06 ± 2.06 mg/dL with continuous; $P = 0.6$; 36 hours: 9.02 ± 1.94 mg/dL with intermittent v 9.17 ± 1.83 mg/dL with continuous; $P = 0.7$; 48 hours: 9.30 ± 1.43 mg/dL with intermittent v 8.93 ± 1.26 mg/dL with continuous; $P = 0.7$).^[17]

The second three-armed RCT (120 preterm infants, birth weight 1250–2000 g, Coombs' negative, no haemolytic anaemia, no gross congenital anomalies, no severe respiratory distress syndrome) compared continuous phototherapy for 5 days versus intermittent phototherapy (12 hours on, 12 hours off) for 5 days or no treatment.^[10] We only report the data on continuous and intermittent groups here. The RCT found no difference between groups in the proportion of preterm infants who had a serum bilirubin level >12 mg/dL (3/40 [8%] with intermittent phototherapy v 2/40 [5%] with continuous phototherapy; P value not reported). However, the RCT found that compared with intermittent phototherapy, a smaller proportion of preterm infants treated with continuous phototherapy had serum bilirubin levels >15 mg/dL (1/40 [3%] with intermittent phototherapy v 0/40 [0%] with continuous phototherapy; P value not reported).^[10]

The third RCT (34 term infants >2500 g, physiological jaundice) compared intermittent equal duration therapy (4 hours on, 4 hours off) versus intermittent short duration phototherapy (1 hour on, 3 hours

off) versus continuous phototherapy.^[18] The RCT found no significant difference in the duration of phototherapy required or total hours of irradiation (duration of phototherapy required: 86.7 ± 28.9 hours with intermittent equal v 100.0 ± 61 hours with intermittent short v 89.9 ± 54.2 hours with continuous; $P > 0.05$; total hours of irradiation: 43.4 ± 14.5 hours with intermittent equal v 25.0 ± 15.3 hours with intermittent short v 89.9 ± 54.2 hours with continuous; $P < 0.05$). The RCT also found no significant difference between groups in the rate of increase of serum bilirubin levels or in the rate of decrease in serum bilirubin levels (rate of increase of serum bilirubin levels: 1.25 ± 0.66 micromol/L/hour with intermittent equal v 0.89 ± 0.65 micromol/L/hour with intermittent short v 0.82 ± 0.43 micromol/L/hour with continuous; $P > 0.05$; rate of decrease in serum bilirubin levels: 1.49 ± 0.87 micromol/L/hour with intermittent equal v 1.09 ± 0.56 micromol/L/hour with intermittent short v 1.08 ± 4.10 micromol/L/hour with continuous; $P > 0.05$).^[18]

Close versus distant light-source phototherapy:

We found one RCT (774 infants, hyperbilirubinaemia not severe enough to require exchange transfusion, absence of history of traditional herbal treatment, absence of treatment with phenobarbital, absence of septicaemia, absence of hepatomegaly regardless of cause, absence of suspected congenital metabolic disorders) comparing conventional phototherapy given from a distance of 20 cm (close light-source) above the neonate versus 40 cm (distant light-source) above the neonate.^[19] The RCT found that close light-source phototherapy significantly reduced the mean duration of treatment compared with distant light-source phototherapy (66 ± 22 hours with close light-source v 81.6 ± 24.6 hours with distant light-source; $P < 0.001$).^[19]

Increased skin exposure versus standard skin exposure phototherapy:

We found one RCT (59 preterm infants at least 36 weeks' gestation, >1500 g birth weight, non-haemolytic hyperbilirubinaemia with total serum bilirubin in range for phototherapy, absence of congenital anomaly, absence of need for respiratory support, absence of co-existing pathology) comparing conventional phototherapy in partially clothed infants (disposable nappy only) versus naked infants.^[20] The RCT found no significant difference between groups in the number of infants still requiring phototherapy between 24 and 48 hours ($13/30$ [43%] with partial clothing v $13/29$ [45%] with naked infants; $P = 0.9$). The RCT also found no significant difference between groups in the number of infants still requiring phototherapy between 48 and 72 hours ($2/30$ [7%] with partial clothing v $4/29$ [14%] with naked infants; $P = 0.4$). The RCT found no significant difference between groups in the mean percentage decline in serum bilirubin levels ($15.4\% \pm 18\%$ with partial clothing v $19.0\% \pm 15\%$ with naked infants; $P = 0.4$). There was also no significant difference between groups in the absolute change in mean serum bilirubin levels (37.6 ± 41 micromol/L with partial clothing v 46.4 ± 37 micromol/L with naked infants; $P = 0.4$).^[20]

Fluorescent lamps versus halide lamps:

We found one three-armed RCT (101 infants, at least 40 hours of age, non-haemolytic hyperbilirubinaemia, not on antibiotics) comparing treatment with 6 standard fluorescent lamps versus fluorescent lamps plus white reflecting curtains versus a halide lamp.^[21] We only report the data from the fluorescent compared with halide lamps here. The RCT found no significant difference between groups in reduction in bilirubin levels per 24 hours (3.3 ± 1.5 mg/dL with fluorescent lamps v 3.2 ± 1.3 mg/dL with halide lamps; $P > 0.05$).

Fluorescent versus blue fluorescent lamps:

We found one three-armed RCT (72 infants, hyperbilirubinaemia in first 72 hours of life, SBR >8.6 mg/dL, no sepsis, no respiratory distress, non-haemolytic) comparing daylight fluorescent lamps versus standard blue fluorescent lamps versus blue fluorescent lamps with a narrow spectral emission.^[22] Phototherapy was discontinued when serum bilirubin concentration had declined steadily for at least 12 hours, and had reached a level of at most 8 mg per 100 mL. The RCT found that a smaller proportion of infants discontinued phototherapy after 1 day with daylight fluorescent lamps compared with blue fluorescent lamps (with or without narrow spectral emission) ($2/24$ [8%] with daylight v $6/24$ [25%] with standard blue v $12/24$ [50%] with narrow spectrum blue; P values not reported).^[22] However, the RCT found similar rates in the number of infants discontinuing phototherapy on days 2 and 3 (day 2: $6/24$ [25%] with daylight v $14/24$ [58%] with standard blue v $8/24$ [33%] with narrow spectrum blue; P values not reported; day 3: $7/24$ [29%] with daylight v $4/24$ [17%] with standard blue v $4/24$ [17%] with narrow spectrum blue; P values not reported). However, the RCT found that compared with daylight fluorescent lamps, blue fluorescent lamps (with or without narrow spectral emission) increased mean decreases in serum bilirubin levels after the first 24 hours, the second 24 hours, and the third 24 hours of phototherapy (mean decrease in the first 24 hours: 0.96 mg/dL with daylight v 2.17 mg/dL with standard blue v 3.52 mg/dL with narrow spectrum blue; P values not reported; mean decrease in the second 24 hours: 0.38 mg/dL with daylight v 1.38 mg/dL with standard blue v 2.32 mg/dL with narrow spectrum blue; P values not reported; mean decrease in the third 24 hours: 1.46 mg/dL with daylight v 1.72 mg/dL with standard blue v 1.82 mg/dL with narrow spectrum blue; P values not reported).^[22]

Blue fluorescent versus green fluorescent lamps:

We found two RCTs comparing blue fluorescent versus green fluorescent light. ^[23] ^[24]

The first RCT (262 infants, non-haemolytic jaundice) compared treatment with blue fluorescent lamps versus green fluorescent lamps. ^[23] The RCT also reported a planned subgroup analysis on term (at least 37 weeks' gestation) versus preterm (<37 weeks' gestation) infants. ^[23] The RCT found no significant difference in the duration of phototherapy in the term infants or preterm infants with blue fluorescent light compared with green fluorescent light (term infants: 49.88 ± 3.02 hours with blue light v 42.68 ± 2.74 hours with green light; $P > 0.05$; preterm infants: 53.29 ± 5.90 hours with blue light v 53.26 ± 5.52 hours with green light; $P > 0.05$). The RCT also found no significant difference in the rate of fall of serum bilirubin in term infants or preterm infants with blue light compared with green light (term infants: 2.86 ± 0.17 micromol/hour with blue light v 3.27 ± 0.22 micromol/hour with green light; $P > 0.05$; preterm infants: 2.50 ± 0.39 micromol/hour with blue light v 2.91 ± 0.38 micromol/hour with green light; $P > 0.05$). ^[23]

The second RCT (84 low birth weight infants, non-haemolytic jaundice, no respiratory distress, no sepsis, no post-phototherapy rebound) compared treatment with blue fluorescent lamps versus green fluorescent lamps. ^[24] The RCT reported a planned subgroup analysis, in which three groups were compared based on initial serum bilirubin levels (group 1: 21–16.1 mg/dL; group 2: 16–12.1 mg/dL; group 3: 12–9.0 mg/dL). ^[24] The RCT found no significant difference in the percentage decrease in serum bilirubin levels for any of the subgroups with blue light compared with green light at 24 and 48 hours (group 1: 24 hours: 31.7% decrease with blue light v 31% decrease with green light; 48 hours: 36% decrease with blue light v 46% decrease with green light; group 2: 24 hours: 22% decrease with blue light v 20.3% decrease with green light; 48 hours: 27% decrease with blue light v 22% decrease with green light; group 3: 24 hours: 20% decrease with blue light v 19% decrease with green light; 48 hours: 16% decrease with blue light v 10.5% decrease with green light; $P > 0.5$ for all comparisons). ^[24]

Blue-green fluorescent versus blue fluorescent lamps:

We found 4 RCTs comparing blue-green fluorescent light versus blue fluorescent light. ^[25] ^[26] ^[27] ^[28]

The first RCT (85 infants, preterm with a gestational age 196–258 days, postnatal age >24 hours, non-haemolytic hyperbilirubinaemia) compared treatment with 6 turquoise (blue-green) fluorescent lamps plus two daylight fluorescent lamps versus 6 blue fluorescent lamps plus two daylight fluorescent lamps. ^[25] The RCT found no significant difference in total serum bilirubin level decrease after 48 hours of treatment with turquoise light compared with blue light ($P = 0.36$; absolute data presented graphically).

The second RCT (141 infants, preterm with a gestational age 196–258 days, postnatal age >24 hours, non-haemolytic hyperbilirubinaemia and no previous phototherapy) compared phototherapy with 8 turquoise fluorescent lamps at an average distance of 41 cm versus phototherapy with 8 blue fluorescent lamps at an average distance of 32 cm. ^[26] The RCT found that compared with blue fluorescent light, turquoise fluorescent light significantly increased the mean decrease in serum bilirubin levels after 24 hours of treatment (mean decrease: 92 ± 31 micromol/L with turquoise light v 78 ± 34 micromol/L with blue light; mean difference 15 micromol/L; $P = 0.008$). ^[26]

The third three-armed RCT (114 jaundiced, but otherwise healthy, term infants) compared 6 focused arrays of blue LED phototherapy, 6 focused arrays of blue-green LED phototherapy, and conventional phototherapy consisting of three halogen-quartz bulbs. ^[27] We only report the data for the blue LED phototherapy compared with blue-green LED phototherapy arms here (47 infants). ^[27] The RCT found no significant difference in the mean number of hours spent under phototherapy with blue-green LED phototherapy compared with blue LED phototherapy (39.2 ± 25.5 hours with blue-green LED v 31.6 ± 19.6 hours with blue LED; P value reported as not significant). The RCT also found no significant difference between groups in the mean rate of serum bilirubin level decline (-1.55 ± 3.54 micromol/L with blue-green LED v -2.82 ± 2.44 micromol/L with blue LED; P value reported as not significant). ^[27]

The fourth RCT (40 infants, low birth weight, hyperbilirubinaemia in first 4 days of life, healthy) compared treatment with blue-green fluorescent lights versus treatment with blue fluorescent lights. ^[28] The RCT found that compared with blue fluorescent light, blue-green fluorescent light significantly reduced the number of infants still requiring phototherapy after 24 hours of treatment (1/20 [5%] with blue-green light v 10/20 [50%] with blue light; $P < 0.0001$). The RCT also found that blue-green fluorescent light significantly increased the mean percentage decrement in serum bilirubin levels after 24 hours of treatment compared with blue fluorescent light (46.4% with blue-green light v 22.6% with blue light; $P < 0.0001$). ^[28]

Blue LED versus conventional quartz-halogen:

We found three RCTs comparing blue LED with conventional phototherapy. ^[29] ^[27] ^[30]

The first RCT (69 infants, jaundiced but otherwise healthy, gestational age >37 weeks) compared phototherapy with 6 focused blue gallium nitride LEDs versus conventional phototherapy with three halogen-quartz bulbs. ^[29] The RCT found no significant difference in the number of hours spent under phototherapy with blue LED compared with conventional phototherapy (31 ± 17 hours with blue LED v 32 ± 17 hours with conventional phototherapy; $P = 0.93$). The RCT also found no significant difference in the rate of serum bilirubin level decline with blue LED compared with conventional phototherapy (-2.87 ± 2.44 micromol/L/hour with blue LED v -2.07 ± 3.03 micromol/L/hour with conventional phototherapy; $P = 0.94$). ^[29]

The second three-armed RCT (114 jaundiced, but otherwise healthy, term infants) compared 6 focused arrays of blue LED phototherapy, 6 focused arrays of blue-green LED phototherapy, and conventional phototherapy consisting of three halogen-quartz bulbs. We only report the data for the blue LED phototherapy versus conventional phototherapy comparison here (82 infants). ^[27] The RCT found no significant difference between groups in the mean number of hours spent under phototherapy (31.6 ± 19.6 hours with blue LED v 35.4 ± 20.2 hours with conventional phototherapy; P value reported as not significant), or in the mean rate of serum bilirubin level decline (-2.82 ± 2.44 micromol/hour with blue LED v -2.42 ± 3.03 micromol/hour with conventional phototherapy; P value reported as not significant). ^[27]

The third RCT (88 preterm infants, birth weight >1000 g, non-haemolytic jaundice, no ecchymosis, no malformations, no congenital infection) compared 5 blue LEDs versus single quartz-halogen phototherapy. ^[30] The RCT found that compared with conventional phototherapy, blue LED phototherapy significantly decreased the mean time spent under phototherapy (36.8 ± 21 hours with blue LED v 63.8 ± 37 hours with conventional phototherapy; $P < 0.01$). The RCT also found that blue LED significantly reduced mean serum bilirubin levels after 8, 16, and 24 hours of treatment compared with conventional phototherapy (8 hours: 9.3 ± 2.5 mg% with blue LED v 10.5 ± 2.1 mg% with conventional; $P < 0.05$; 16 hours: 8.1 ± 2.7 mg% with blue LED v 9.4 ± 1.8 mg% with conventional; $P < 0.01$; 24 hours: 7.2 ± 2.5 mg% with blue LED v 9.6 ± 2.4 mg% with conventional; $P < 0.01$). ^[30]

Blue LED versus blue fluorescent lamps:

We found one RCT (66 healthy infants, at least 35 weeks' gestation) that compared phototherapy using blue LED (overhead neoBLUE LED plus either BiliBlanket or Wallaby system underneath) versus phototherapy with blue fluorescent light (8 overhead blue fluorescent lights plus either BiliBlanket or Wallaby system underneath). ^[31] The RCT found no significant difference in the mean rate of serum bilirubin level decline with blue LED compared with blue fluorescent phototherapy (0.35 ± 0.25 mg/dL/hour with blue LED v 0.27 ± 0.25 mg/dL/hour with blue fluorescent phototherapy; $P = 0.20$). ^[31]

Blue-green LED versus conventional quartz-halogen:

We found one three-armed RCT (114 jaundiced, but otherwise healthy, term infants) comparing 6 focused arrays of blue LED phototherapy, 6 focused arrays of blue-green LED phototherapy, and conventional phototherapy consisting of three halogen-quartz bulbs. ^[27] We only report the data for the blue-green LED phototherapy versus conventional phototherapy comparison here (79 infants). The RCT found no significant difference in the mean number of hours spent under phototherapy (39.2 ± 25.5 hours with blue-green light v 35.4 ± 20.2 hours with conventional phototherapy; P value reported as not significant) or in the mean rate of serum bilirubin level decline (-1.55 ± 3.54 micromol/hour with blue-green light v -2.42 ± 3.03 micromol/hour with conventional phototherapy; P value reported as not significant) with blue-green LED phototherapy compared with conventional phototherapy. ^[27]

Prophylactic phototherapy versus threshold phototherapy:

We found one RCT (95 infants, birth weight <1500 g, within 12 hours of birth, without isoimmunisation or major life-threatening anomaly) that compared prophylactic phototherapy (commencement of phototherapy within 12 hours of birth) versus threshold phototherapy (commencement once SBR >150 micromol/L). ^[32] The RCT found no significant difference between groups in the combined outcome of death and cerebral palsy at 18 months (5/40 [13%] with prophylactic phototherapy v 10/43 [23%] with threshold phototherapy; OR 1.86, 95% CI 0.58 to 5.92; $P = 0.4$). The RCT also found no significance between groups in the incidence of cerebral palsy or in the incidence of abnormal developmental index score at 18 months (cerebral palsy: 2/37 [5%] with prophylactic phototherapy v 5/38 [12%] with threshold phototherapy; OR 2.43, 95% CI 0.44 to 13.34; $P = 0.44$; abnormal developmental index score <84: 9/37 [24%] with prophylactic phototherapy v 8/38 [21%] with threshold phototherapy; OR 0.87, 95% CI 0.30 to 2.48; $P = 0.78$). The RCT found no significant difference in the mean number of hours of phototherapy or in the mean total of days in neonatal

intensive care unit with prophylactic compared with threshold phototherapy (mean number of hours of phototherapy: 85 hours with prophylactic phototherapy v 68.5 hours with threshold phototherapy; $P > 0.05$; mean total of days in neonatal intensive care unit: 82.3 ± 37.9 days with prophylactic phototherapy v 82.7 ± 38.9 days with threshold phototherapy; $P > 0.05$).^[32]

The RCT found no significant difference in the peak unconjugated serum bilirubin levels between groups (170 ± 26.0 micromol/L with prophylactic phototherapy v 183.5 ± 28.0 micromol/L with threshold phototherapy; $P > 0.05$); however, a subgroup analysis of infants with a birth weight < 1000 g found that compared with threshold phototherapy, prophylactic phototherapy significantly reduced peak unconjugated serum bilirubin levels (139.2 ± 46.0 micromol/L with prophylactic phototherapy v 171.2 ± 26.0 micromol/L with threshold phototherapy; $P < 0.02$).^[32] A further subgroup analysis of infants with a birth weight of 1000 g to 1499 g found no significant difference between groups in peak unconjugated serum bilirubin level (190.6 ± 40.8 micromol/L with prophylactic phototherapy v 191.9 ± 26.5 micromol/L with threshold phototherapy; $P > 0.05$). The RCT found that compared with threshold phototherapy, prophylactic phototherapy significantly reduced the number of infants whose peak serum bilirubin level was reached before 48 hours of age (1/45 [2%] with prophylactic phototherapy v 14/47 [30%] with threshold phototherapy; $P < 0.001$).^[32]

Low threshold versus high threshold phototherapy:

We found two RCTs comparing low threshold versus high threshold phototherapy.^{[33] [34]}

The first RCT (1974 infants, extremely low birth weight, 12–36 hours old, absence of terminal condition, absence of previous phototherapy, absence of major congenital anomaly, non-severe haemolytic disease, absence of congenital non-bacterial infection) compared low threshold phototherapy (initiation of phototherapy at enrolment, SBR expected to be 85 micromol/L and recommencement of phototherapy if SBR > 85 micromol/L in first 7 days of life or SBR > 137 micromol/L from day 7–14 of life) versus high threshold phototherapy (initiation of phototherapy at 137 micromol/L and recommencement if SBR > 137 micromol/L in first 7 days and SBR > 171 micromol/L from day 7–14 of life).^[33]

The RCT found no significant difference between groups in mortality before day 15 or mortality before discharge (mortality before day 15: 96/990 [9.7%] with low threshold v 95/984 [9.7%] with high threshold; RR 1.00, 95% CI 0.88 to 1.30; mortality before discharge: 209/990 [21%] with low threshold v 201/984 [20%] with high threshold; RR 1.03, 95% CI 0.88 to 1.21).^[33] The RCT also found no significant difference between groups in mortality or mortality and neurodevelopmental impairment at 18 to 22 months (mortality: 230/946 [24%] with low threshold v 218/944 [23%] with high threshold; RR 1.05, 95% CI 0.90 to 1.22; mortality and neurodevelopmental impairment: 465/902 [52%] with low threshold v 493/902 [55%] with high threshold; RR 0.94, 95% CI 0.87 to 1.02).

The RCT found that compared with high threshold phototherapy, low threshold phototherapy significantly reduced the risk of neurodevelopmental impairment and profound impairment at 18 to 22 months (neurodevelopmental impairment: 235/902 [26%] with low threshold v 275/902 [30%] with high threshold; RR 0.86, 95% CI 0.74 to 0.99; MDI score for profound impairment: 22 infants with a score of 50, 121 infants with a score of < 50) (80/895 [9%] with low threshold v 119/896 [13%] with high threshold; RR 0.68, 95% CI 0.52 to 0.89).^[33] However, the RCT found no significant difference between groups in cerebral palsy at 18 to 22 months (mild/moderate or severe: 81/929 [9%] with low threshold v 91/924 [10%] with high threshold; RR 0.89, 95% CI 0.67 to 1.18).

The RCT found that low threshold phototherapy significantly reduced the risk of severe hearing loss compared with high threshold phototherapy at 18 to 22 months (9/925 [1%] with low threshold v 28/922 [3%] with high threshold; RR 0.32, 95% CI 0.15 to 0.98). It found no significant difference in blindness compared with high threshold phototherapy at 18 to 22 months (2/928 [0.2%] with low threshold v 7/924 [0.8%] with high threshold; RR 0.28, 95% CI 0.06 to 1.37).^[33]

The RCT found that low threshold phototherapy significantly increased the duration of phototherapy compared with high threshold phototherapy (88 ± 48 hours with low threshold v 35 ± 31 hours with high threshold; $P < 0.001$). However, it found no significant difference between groups in the number of exchange transfusions or length of hospital stay (exchange transfusions: 2 with low threshold v 3 with high threshold; $P = 0.69$; length of hospital stay: 97 ± 43 days with low threshold v 100 ± 47 days with high threshold; $P = 0.11$).^[33] The RCT found that low threshold phototherapy significantly decreased the serum bilirubin level at day 5 compared with high threshold phototherapy (0.33 ± 0.25 mg/dL with low threshold v 0.48 ± 0.33 mg/dL with high threshold; $P < 0.001$).^[33]

The second RCT (78 infants, birth weight < 2500 g) compared starting phototherapy once serum bilirubin levels were > 13 mg/dL versus starting phototherapy once serum bilirubin levels were

10 mg/dL or more and treating for 12 hours versus starting phototherapy once serum bilirubin levels were 10 mg/dL or more and treating for 24 hours. ^[34]

The RCT found no difference in the number of infants requiring phototherapy at <72 hours of age (14/26 [54%] with higher threshold v 17/29 [59%] with lower threshold and 12 hours of phototherapy v 9/23 [39%] with lower threshold and 24 hours of phototherapy; P values not reported). ^[34]

The RCT also found no difference in the number of infants who received phototherapy in the first 72 hours of life and then required additional phototherapy (8/14 [57%] with higher threshold v 6/17 [35%] with lower threshold and 12 hours of phototherapy v 2/9 [22%] with lower threshold and 24 hours of phototherapy; P values not reported). ^[34]

The RCT found no difference in the number of infants requiring phototherapy at 72 hours of age or more (12/26 [46%] with higher threshold v 12/29 [41%] with lower threshold and 12 hours of phototherapy v 14/23 [61%] with lower threshold and 24 hours of phototherapy; P values not reported). ^[34]

The RCT found no difference in the number of infants who received phototherapy after 72 hours of age and required additional phototherapy (3/12 [25%] with higher threshold v 1/12 [8%] with lower threshold and 12 hours of phototherapy v 2/14 [8%] with lower threshold and 24 hours of phototherapy; P values not reported). ^[34]

Compact fluorescent light phototherapy versus standard length tube light phototherapy:

We found one RCT (100 infants >34 weeks' gestation, haemolytic jaundice excluded), which found no significant difference between compact fluorescent light (CFL) and standard length tube light (STL) phototherapy in total duration of treatment required (40.66 hours with CFL v 40.78 hours with STL; P = 0.98). It found that CFL significantly reduced the mean total serum bilirubin over 12 hours compared with STL (15.86 mg/dL, 95% CI 15.5 mg/dL to 16.2 mg/dL with CFL v 14.23 mg/dL, 95% CI 13.7 mg/dL to 14.8 mg/dL with STL; P <0.001). ^[35]

Phototherapy versus immunoglobulin:

See [benefits of immunoglobulin](#), p 20 .

Harms:

Conventional phototherapy versus no treatment:

The review found no evidence that phototherapy for neonatal hyperbilirubinaemia has any long-term adverse neurodevelopmental effects. ^[3]

Continuous phototherapy versus no treatment:

The RCT found that a significantly higher proportion of preterm infants in the control group regained or surpassed their birth weight compared with infants treated with continuous phototherapy at postnatal day 7 (44% with continuous phototherapy v 80% with no treatment; reported as significant; P value not reported). ^[10] However, the RCT found that infants treated with continuous phototherapy gained significantly more weight in the second and third postnatal weeks compared with infants in the control group (second postnatal week: 184.5 ± 55.5 g with continuous phototherapy v 139.0 ± 69.8 g with no treatment; P <0.05; third postnatal week: 225.3 ± 62.5 g with continuous phototherapy v 162.4 ± 62.3 g with no treatment; P <0.05). ^[10]

Intermittent phototherapy versus no treatment:

The RCT found that a significantly higher proportion of preterm infants in the control group regained or surpassed their birth weight compared with infants treated with intermittent phototherapy at postnatal day 7 (57.6% with intermittent phototherapy v 80% with no treatment; reported as significant; P value not reported). ^[10] However, the RCT found that infants treated with intermittent phototherapy gained significantly more weight in the second and third postnatal weeks compared with infants in the control group (second postnatal week: 193.6 ± 82.3 g with intermittent phototherapy v 139.0 ± 69.8 g with no treatment; P <0.05; third postnatal week: 195.5 ± 74.2 g with intermittent phototherapy v 162.4 ± 62.3 g with no treatment; P <0.05). ^[10]

Fibreoptic phototherapy versus no treatment:

The review gave no information on adverse effects for this comparison. ^[11]

Conventional versus fibreoptic phototherapy:

In the systematic review, one small trial (20 infants) found that transepidermal water loss (sweating) was significantly higher in infants treated with fibreoptic devices compared with conventional phototherapy, and one small trial (34 infants) found no significant difference between fibreoptic and conventional phototherapy in mothers developing migraine during their infants' treatment with phototherapy. ^[11] However, the clinical significance of this is uncertain. One RCT reported transient erythema and mild watery stools not leading to dehydration (erythema: 1/50 [2%] with conventional

v 1/50 [2%] with fibreoptic; mild watery stools: 3/50 [6%] with conventional v 3/50 [6%] with fibreoptic).^[12] A subsequent RCT found similar levels of transient erythema between conventional phototherapy, fibreoptic Wallaby phototherapy, and fibreoptic BiliBlanket phototherapy (10/35 [29%] with conventional v 9/35 [26%] with Wallaby v 8/35 [23%] with BiliBlanket; significance not assessed).^[13]

Double versus single phototherapy:

One RCT found no significant difference between double conventional and single conventional phototherapy in weight reduction, frequency of stooling, or fever.^[14] Another RCT found a small increase in rates of transient erythema using the combination of Wallaby and conventional phototherapy compared with one type of phototherapy (12/35 [34%] with combined v 10/35 [29%] with conventional v 9/35 [26%] with Wallaby v 8/35 [23%] with BiliBlanket; significance not assessed).^[13] The third subsequent RCT found that double surface phototherapy significantly increased body temperature compared with single surface phototherapy after 24 hours of treatment ($37.1 \pm 0.2^\circ\text{C}$ with double surface phototherapy v $36.9 \pm 0.3^\circ\text{C}$ with single surface phototherapy; $P = 0.003$).^[15] The RCT also found that double surface phototherapy significantly lowered the number of stools per day compared with single surface phototherapy (4.3 ± 3.0 stools/day with double surface phototherapy v 7.2 ± 3.4 stools/day with single surface phototherapy; $P = 0.001$). The RCT found no significant difference between groups in body weight at 24 and 48 hours after phototherapy commenced, percent body weight change at 24 and 48 hours after phototherapy commenced, or temperature after 48 hours of phototherapy (body weight at 24 hours: 3021.7 g with double surface phototherapy v 2971.7 g with single surface phototherapy; $P = 0.52$; body weight at 48 hours: 3043.3 g with double surface phototherapy v 3010.7 g with single surface phototherapy; $P = 0.69$; percent body weight change at 24 hours: 1% with double surface phototherapy v 1.5% with single surface phototherapy; $P = 0.46$; percent body weight change at 48 hours: 1.7% with double surface phototherapy v 2.3% with single surface phototherapy; $P = 0.44$; temperature after 48 hours: $36.9 \pm 0.2^\circ\text{C}$ with double surface phototherapy v $36.9 \pm 0.2^\circ\text{C}$ with single surface phototherapy; $P = 0.13$).^[15]

Triple versus double phototherapy:

The RCT gave no information on adverse effects.^[16]

Intermittent versus continuous phototherapy:

The RCTs gave no information on adverse effects.^{[10] [17] [18]}

Close versus distant light-source phototherapy:

The RCT found no significant difference in adverse effects such as troublesome skin rashes, burns, clinical dehydration, or lethargy between close and distant phototherapy (no further data reported).^[19]

Increased skin exposure versus standard skin exposure phototherapy:

The RCT found no significant difference between phototherapy groups treated partially clothed (disposable nappy only) or naked in the incidence of the following Parenting Stress Index scores: 'parental distress', 'parent-child dysfunction' (1/25 [4%] with partial clothing v 3/25 [12%] with naked infants; $P = 0.3$), 'parent-child dysfunction', 'difficult child', or 'total stress score' ('parental distress': 6/25 [24%] with partial clothing v 9/25 [36%] with naked infants; $P = 0.4$; 'difficult child': 4/25 [16%] with partial clothing v 3/25 [12%] with naked infants; $P = 0.7$; 'total stress score': 7/25 [28%] with partial clothing v 7/25 [28%] with naked infants; $P = 1$).^[20] The RCT also reported no significant difference between groups in the incidence of rebound jaundice requiring phototherapy (7/30 [23%] with partial clothing v 9/29 [31%] with naked infants; $P = 0.5$). The RCT reported that there were no episodes of patent ductus arteriosus, skin rashes, or dehydration in phototherapy groups treated either partially clothed (disposable nappy only) or naked.^[20]

Fluorescent lamps versus halide lamps:

The RCT gave no information on adverse effects.^[21]

Fluorescent versus blue fluorescent lamps:

The RCT gave no information on adverse effects.^[22]

Blue fluorescent versus green fluorescent lamps:

The RCTs gave no information on adverse effects.^{[23] [24]}

Blue-green fluorescent versus blue fluorescent lamps:

The first two RCTs^{[25] [26]} reported that there were no adverse effects apart from "loose green stools". However, it is unclear as to the number of babies who had this adverse effect and in what treatment allocation group they were. The third RCT reported that no adverse effects were noted.^[27] The fourth RCT gave no information about adverse effects.^[28]

Blue LED versus conventional quartz-halogen:

The first and second RCTs reported that there were no adverse effects in either group. ^[29] ^[27]

The third RCT reported that no one in either group required exchange transfusion, developed rashes, or had temperature instability. ^[30] It also found no significant difference between groups in weight loss or in the incidence of rebound jaundice (weight loss: 1.89% of weight loss against initial weight with blue LED and 1.99% of weight loss against initial weight with conventional phototherapy; $P = 0.33$; rebound jaundice: 26.8% with blue LED v 18.2% with conventional phototherapy; $P = 0.43$). ^[30]

Blue LED versus blue fluorescent lamps:

The RCT gave no information on adverse effects. ^[31]

Blue-green LED versus conventional quartz-halogen:

The RCT reported that no adverse effects were found. ^[27]

Prophylactic phototherapy versus threshold phototherapy:

The RCT found no significant difference between groups in the incidence of percentage weight loss, mean days to regain birth weight, incidence of intraventricular haemorrhage, incidence of periventricular leukomalacia, incidence of retinopathy of prematurity greater than stage 2, or rebound phototherapy (weight loss: $12.1\% \pm 4.9\%$ with prophylactic phototherapy v $11\% \pm 5.0\%$ with threshold phototherapy; $P > 0.05$; mean days to regain birth weight: 11.8 ± 3.9 days with prophylactic phototherapy v 11 ± 4.0 days with threshold phototherapy; $P > 0.05$; intraventricular haemorrhage: 15/43 [35%] with prophylactic phototherapy v 14/44 [32%] with threshold phototherapy; $P > 0.05$; periventricular leukomalacia: 2/43 [4.7%] with prophylactic phototherapy v 2/44 [4.5%] with threshold phototherapy; $P > 0.05$; retinopathy of prematurity >stage 2: 7/43 [16%] with prophylactic phototherapy v 11/44 [25%] with threshold phototherapy; $P > 0.05$; rebound phototherapy (18/45 [40%] with prophylactic phototherapy v 12/47 [26%] with threshold phototherapy; $P > 0.05$). ^[32]

Low threshold versus high threshold phototherapy:

The first RCT found no significant difference between groups in patent ductus arteriosus (556/990 [56%] with low threshold v 582/984 [59%] with high threshold; RR 0.95, 95% CI 0.88 to 1.02), or necrotising enterocolitis (105/990 [11%] with low threshold v 117/984 [12%] with high threshold; RR 0.90, 95% CI 0.79 to 1.14). ^[33] The second RCT gave no information on adverse effects. ^[34]

Compact fluorescent light versus standard length tube light phototherapy:

One RCT found no significant difference in moderate or extreme eye pain caused by glare, moderate or extreme giddiness, and moderate or extreme headache in nursing staff with compact fluorescent light (CFL) compared with standard length tube light (STL; pain from glare: 38% with CFL v 48% with STL; $P = 0.16$; giddiness: 14% with CFL v 20% with STL; $P = 0.42$; headache: 6% with CFL v 8% with STL; $P = 1$). ^[35]

Phototherapy versus immunoglobulin:

See harms of immunoglobulin, p 20 .

Comment:**Conventional phototherapy:**

The largest RCT comparing phototherapy with no treatment did not use very intensive phototherapy, which probably explains why phototherapy seemed no better than control in preventing exchange transfusion in the haemolytic subgroup. ^[6] The RCT of 4 interventions for jaundice in breastfed newborns allocated the infants to the groups at random, although there were more infants entered into the groups with phototherapy as one of the interventions. ^[7] This apparent imbalance was not explained in the text and, therefore, may limit the validity of its conclusions.

Fibreoptic phototherapy:

The systematic review of fibreoptic phototherapy also included quasi-randomised controlled trials, all of which used alternate or sequential allocation. ^[11] This may limit the validity of its conclusions. Two different fibreoptic devices were used by trials included in the review: BiliBlanket and Wallaby. The irradiance of the Wallaby phototherapy system and BiliBlanket are different, and the irradiance setting of the BiliBlanket was not the same in different trials. ^[11] Conventional phototherapy varied between trials, with trials using either halogen or fluorescent lamps, emitting white light, blue light, or a mixture of the two. ^[11] Inclusion criteria in the trials varied, with some excluding infants with haemolysis and others including them. No trials including infants with haemolysis reported separate data for this group, and the review was unable to do a planned subgroup analysis on this group. ^[11] Phototherapy was instituted at different serum bilirubin levels in different trials; this review has not addressed the complex question of the bilirubin level at which to commence phototherapy. Outcomes of trials included in the review were reported mainly in terms of changes in serum bilirubin levels; the incidence of kernicterus was not reported in any of the trials, although very large studies would be required to show a reduction in such a rare adverse event. ^[11] No trials were

identified to support or refute the view that fiberoptic devices interfere less with infant care or impact less on parent–child bonding. ^[11]

Clinical guide:

It is generally accepted that intensive phototherapy applied to reduce the bilirubin levels rapidly (rather than merely to prevent levels rising further) has greatly reduced the need for exchange transfusions in infants with or without haemolysis.

OPTION EXCHANGE TRANSFUSION

Duration of treatment

Single volume exchange compared with double volume exchange We don't know whether single volume exchange and double volume exchange differ in effectiveness at reducing the mean duration of phototherapy after exchange transfusion as we found insufficient evidence from one small RCT of 20 infants with hyperbilirubinaemia secondary to ABO incompatibility (low-quality evidence).

Serum bilirubin levels

Single volume exchange compared with double volume exchange We don't know whether single volume exchange and double volume exchange differ in effectiveness at reducing the immediate post-exchange mean serum bilirubin level as we found insufficient evidence from one small RCT of 20 infants with hyperbilirubinaemia secondary to ABO incompatibility (low-quality evidence).

Note

We found no direct evidence from RCTs comparing the effects of exchange transfusion versus no active treatment. There is general consensus that exchange transfusion is effective in reducing serum bilirubin levels and preventing neurodevelopmental sequelae. It is generally accepted that this procedure will reduce serum bilirubin levels when other interventions such as phototherapy have failed to control the rise in serum bilirubin. However, exchange transfusion is not without risks.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits:

Exchange transfusion versus no treatment:

We found no systematic review or RCTs (see comment below).

Exchange transfusion versus phototherapy:

We found no systematic review or RCTs.

Single versus double volume exchange transfusion:

We found one systematic review (search date 2006) comparing single volume exchange transfusion (SVET) versus double volume exchange transfusion (DVET). ^[36] The review included only one RCT (20 full-term infants, hyperbilirubinaemia secondary to ABO incompatibility, no perinatal asphyxia, no congenital malformation, no suspected or confirmed sepsis, no respiratory distress, no hyperbilirubinaemia secondary to maternal drugs, no polycythaemia, no skin haematomas, no cephalhaematoma). ^[37] The review found no significant difference between groups in mean duration of phototherapy after exchange transfusion (45.4 ± 17.7 hours with SVET v 38.1 ± 16.4 hours with DVET; $P > 0.05$) or in the immediate post-exchange mean serum bilirubin level (130 ± 24 micromol/L with SVET v 143 ± 47 micromol/L with double volume; $P > 0.05$). ^[36]

Harms:

Exchange transfusion versus no treatment:

We found no RCTs.

Exchange transfusion versus phototherapy:

We found no RCTs.

Single versus double volume exchange transfusion:

The review found no significant difference in the rebound increase in serum bilirubin levels after exchange transfusion (64.9 ± 16.7 micromol/L with SVET v 73.7 ± 41.4 micromol/L with DVET; $P > 0.05$). ^[36] However, the review reported that compared with DVET, SVET significantly increased post-exchange platelet levels (reported as significant; P value not reported). The review also reported that DVET significantly increased the immediate post-exchange haemoglobin levels compared with SVET (18.3 g/dL with SVET v 20.4 g/dL with DVET; $P < 0.01$). However, the review found no significant difference in the platelet levels or haemoglobin 10 days after exchange transfusion (platelet levels: WMD +24.00, 95% CI –52.66 to +100.66; haemoglobin levels: WMD +0.20, 95% CI –0.81 to +1.21). ^[36]

Comment:

In most of the RCTs comparing other interventions, exchange transfusion was used as an outcome measure.

Clinical guide:

There is general consensus that exchange transfusion is effective in reducing serum bilirubin levels and preventing neurodevelopmental sequelae. It is generally accepted that this procedure will reduce serum bilirubin levels when other interventions such as phototherapy have failed to control the rise in serum bilirubin. Exchange transfusion is not without risks. It has an estimated mortality of 3 to 4 per 1000 exchanged infants, and an estimated range of 5% to 10% permanent sequelae in survivors (aortic thrombosis, intraventricular haemorrhage, pulmonary haemorrhage).^[3] There is insufficient evidence to support the practice of SVET and the current practice of DVET should be continued.

OPTION ALBUMIN INFUSION

We found no clinically important results from RCTs about the effects of albumin infusion in babies with neonatal jaundice.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits: **Albumin infusion versus no treatment:**
We found no systematic review or RCTs.

Albumin infusion versus other treatment:
We found no systematic review or RCTs.

Harms: **Albumin infusion versus no treatment:**
We found no RCTs.

Albumin infusion versus other treatment:
We found no RCTs.

Comment: None.

OPTION HOME PHOTOTHERAPY

We found no clinically important results from RCTs about the effects of home phototherapy in babies with neonatal jaundice.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits: **Home phototherapy versus no treatment:**
We found no systematic review or RCTs.

Home phototherapy versus hospital phototherapy:
We found one systematic review (search date 2003), which identified no RCTs.^[38]

Harms: **Home phototherapy versus no treatment:**
We found no RCTs.

Home phototherapy versus hospital phototherapy:
We found no RCTs.

Comment: None.

OPTION TIN-MESOPORPHYRIN**Neurological/neurodevelopmental delay**

Compared with standard treatment We found insufficient evidence to draw reliable conclusions on the long-term effects of tin-mesoporphyrin on developmental outcomes (*very low-quality evidence*).

Duration of treatment

Compared with standard treatment One study suggested that tin-mesoporphyrin may be more effective than no treatment at reducing the need for phototherapy in term infants with haemolysis excluded whose bilirubin level was raised at 48 to 96 hours after birth to a level likely to require phototherapy. Another study suggested that tin-mesoporphyrin given prophylactically within 24 hours of birth may be more effective than placebo at reducing the number of hours of phototherapy needed in preterm infants with no haemolysis. However, evidence was very weak (*very low-quality evidence*).

Serum bilirubin levels

Compared with standard treatment One study suggested that tin-mesoporphyrin given prophylactically within 24 hours of birth may be more effective than placebo at reducing mean peak bilirubin levels in preterm infants with no haemolysis. However, evidence was very weak (very low-quality evidence).

Note

Tin-mesoporphyrin is not currently licensed for routine clinical use in the UK or US. Further long-term studies are needed to confirm the place of tin-mesoporphyrin in clinical practice.

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits:

Tin-mesoporphyrin versus standard treatment:

We found two RCTs^[39] ^[40] and one non-systematic review of 5 RCTs,^[41] none of which assessed primary outcomes of this review.

In the first RCT (84 term infants, haemolysis excluded), infants were given either tin-mesoporphyrin 6 micromol/kg or no treatment if the bilirubin level was raised at 48 to 96 hours after birth to a level likely to require phototherapy (250–308 micromol/L).^[39] In both groups, phototherapy was commenced if the bilirubin level subsequently exceeded 331 micromol/L, and was discontinued when below 230 micromol/L. The RCT found that tin-mesoporphyrin significantly reduced the need for phototherapy compared with no treatment (infants requiring phototherapy: 0/40 [0%] with tin-mesoporphyrin v 12/44 [27%] with no treatment; $P = 0.0004$).

Similarly, in the second RCT (open label, 86 infants, stratified into 44 term [38–42 weeks] and 42 near term [35–37 weeks], excluding haemolytic jaundice), infants 36 to 84 hours of age received either tin-mesoporphyrin 6 micromol/kg or phototherapy for treatment of hyperbilirubinaemia; phototherapy was started in the group treated initially with tin-mesoporphyrin if serum bilirubin levels exceeded levels outlined in a strict protocol.^[40] The RCT found that none of the infants (0/44) who received tin-mesoporphyrin required supplemental phototherapy. In the phototherapy group, the mean length of phototherapy required was less for term infants than near-term infants (term infants: 33.2 hours; $P < 0.001$; near-term infants: 48.6 hours; $P < 0.03$).

The non-systematic review of 5 RCTs undertaken in the same hospital over a 4-year period compared tin-mesoporphyrin given as prophylaxis within 24 hours of birth (range: 1–6 micromol/kg) versus placebo (517 infants, 454 analysed, stratified into preterm infants <37 weeks, birth weight 1.5–2.5 kg, and preterm infants 30–35 weeks; excluding cases of known haemolysis).^[41] Phototherapy was commenced if the bilirubin level exceeded 212 micromol/L. It found that tin-mesoporphyrin 6 micromol/kg was the most effective dose (between the range 1–6 micromol/kg) to significantly reduce the mean peak bilirubin concentration compared with placebo (160 micromol/L with tin-mesoporphyrin v 197 micromol/L with placebo; 41% reduction; $P < 0.01$). Tin-mesoporphyrin 6 micromol/kg significantly reduced the number of hours of phototherapy required for each infant compared with placebo (47.8 hours with tin-mesoporphyrin v 77.4 hours with placebo; 76% reduction; $P < 0.01$). Follow-up at 3 and 18 months did not show any significant difference in growth or development between tin-mesoporphyrin and usual care in 336 infants who attended both 3-month and 18-month assessments. The meta-analysis undertaken by the non-systematic review was sponsored by the manufacturer.^[41]

Harms:

Tin-mesoporphyrin versus standard treatment:

One non-systematic review of 5 RCTs found that phototherapy produced a mild, transient, non-dose dependent erythema in a few infants treated either with or without tin-mesoporphyrin (2/127 [2%] with phototherapy alone v 13/262 [5%] with tin-mesoporphyrin [129 of these infants also received phototherapy]).^[41]

Comment:

Tin-mesoporphyrin is not currently licensed for routine clinical use in the UK or US. All of the RCTs assessed developmental follow-up, but follow-up data were only reported for 49% of infants. The studies were also limited because tin-mesoporphyrin was used to prevent or reduce the need for phototherapy. Additionally, none of the primary outcomes for this review were assessed by the RCTs included.

Clinical guide:

Further long-term studies are needed to confirm the place of tin-mesoporphyrin in clinical practice.

OPTION

IMMUNOGLOBULIN

New

Need for exchange transfusion

Immunoglobulin compared with phototherapy Intravenous immunoglobulin for 3 consecutive days may be more effective than phototherapy (continuous or intermittent blue light exposure in analysis) at reducing the rate of exchange transfusion (further details not reported) in neonates diagnosed with ABO haemolytic disease of the newborn (ABO-

HDN), mother with blood type O, anti-A/B valence $>1:128$, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia ([very low-quality evidence](#)).

Immunoglobulin plus phototherapy compared with phototherapy alone Intravenous immunoglobulin plus phototherapy seems more effective than phototherapy alone at reducing the proportion of infants with exchange transfusion and the average number of transfusions per infant. Intravenous immunoglobulin plus phototherapy prophylaxis (defined as use in infants with evidence of isoimmune haemolysis within the first few hours of life, before bilirubin has been shown to rise) seems more effective than phototherapy alone at reducing the proportion of infants with exchange transfusion and the average number of transfusions per infant ([moderate-quality evidence](#)).

Duration of treatment

Immunoglobulin compared with no treatment A single dose of intravenous immunoglobulin in the first 24 hours of life may be more effective than no treatment at reducing the need for phototherapy in infants who are Rh positive, with a history of Rh-positive sibling, O-type maternal blood group, positive direct Coombs' test, birth weight 2500 g or above, with no other cause of haemolysis and hyperbilirubinaemia ([low-quality evidence](#)).

Immunoglobulin compared with phototherapy Intravenous immunoglobulin for 3 consecutive days may be more effective than phototherapy (continuous or intermittent blue light exposure in analysis) at reducing the duration of phototherapy in neonates diagnosed with ABO-HDN, mother with blood type O, anti-A/B valence $>1:128$, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia ([low-quality evidence](#)).

Immunoglobulin plus phototherapy compared with phototherapy alone Intravenous immunoglobulin plus phototherapy seems more effective than phototherapy alone at reducing the duration of phototherapy ([moderate-quality evidence](#)).

Serum bilirubin levels

Immunoglobulin compared with no treatment A single dose of intravenous immunoglobulin in the first 24 hours of life may be more effective than no treatment at reducing the increase in serum bilirubin levels (not further defined) in infants who are Rh positive, with a history of Rh-positive sibling, O-type maternal blood group, positive direct Coombs' test, birth weight 2500 g or above, with no other cause of haemolysis and hyperbilirubinaemia ([low-quality evidence](#)).

Immunoglobulin compared with phototherapy Intravenous immunoglobulin for 3 consecutive days may be more effective than phototherapy (continuous or intermittent blue light exposure in analysis) at lowering serum bilirubin levels and increasing the drop in serum bilirubin levels at 3 days in neonates diagnosed with ABO-HDN, mother with blood type O, anti-A/B valence $>1:128$, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, and with clinical symptoms of haemolysis, jaundice, and anaemia ([low-quality evidence](#)).

Immunoglobulin plus phototherapy compared with phototherapy alone Intravenous immunoglobulin plus phototherapy seems more effective than phototherapy alone at reducing maximum serum bilirubin levels; however, results varied by the specific subgroup analysed. We don't know whether intravenous immunoglobulin plus phototherapy prophylaxis (defined as use in infants with evidence of isoimmune haemolysis within the first few hours of life, before bilirubin has been shown to rise) is more effective than phototherapy alone at reducing maximum serum bilirubin levels ([moderate-quality evidence](#)).

For GRADE evaluation of interventions for neonatal jaundice, see table, p 26 .

Benefits:

Immunoglobulin versus no treatment:

We found one RCT (40 infants, Rh positive, history of Rh-positive sibling, O-type maternal blood group, positive direct Coombs' test, birth weight 2500 g or above, no other cause of haemolysis and hyperbilirubinaemia, no birth injury or asphyxia, no family history of haemolytic disorder, no history of intrauterine infections, no extensive bruising or haematoma) comparing intravenous immunoglobulin (single dose of 500 mg/kg) in the first 24 hours of life with no treatment. ^[42] The RCT found that compared with no treatment, intravenous immunoglobulin significantly reduced need for phototherapy, duration of hospital stay, and increase in serum bilirubin levels (need for phototherapy: 0% with intravenous immunoglobulin v 35% with control; $P = 0.008$; duration of hospital stay: reported as significant; P value not reported; increase in serum bilirubin levels: $P = 0.0004$, no further data reported). ^[42]

Immunoglobulin versus phototherapy:

We found one RCT (121 neonates diagnosed with ABO haemolytic disease of the newborn [ABO-HDN], mother with blood type O, anti-A/B valence $>1:128$, blood type A or B of the infant, positive Coombs' test and/or positive free antibody test and/or positive antibody release test, methaemoglobin reduction percentage $>75\%$, clinical symptoms of haemolysis, jaundice, and anaemia) comparing intravenous immunoglobulin (400 mg/kg for 3 consecutive days) versus continuous or intermittent

blue light exposure.^[43] The RCT found that compared with phototherapy, intravenous immunoglobulin significantly reduced the rate of exchange transfusion ($P < 0.01$, no further data reported). The RCT also found that intravenous immunoglobulin significantly lowered the serum bilirubin levels (153.42 micromol/L with intravenous immunoglobulin v 232.54 micromol/L with phototherapy; $P < 0.01$), and significantly increased the daily drop in serum bilirubin levels (56.49 micromol/L with intravenous immunoglobulin v 31.02 micromol/L with phototherapy; $P < 0.01$) compared with phototherapy on day 3 after treatment. The RCT found that intravenous immunoglobulin significantly reduced the duration of phototherapy compared with phototherapy (3.01 hours with intravenous immunoglobulin v 5.41 hours with phototherapy; $P < 0.01$).^[43]

Immunoglobulin plus phototherapy versus phototherapy alone:

We found one systematic review^[44] and two subsequent RCTs^[45] ^[46] that compared immunoglobulin plus phototherapy versus phototherapy alone.

The review (search date 2002, 3 RCTs, 189 infants) found that compared with phototherapy alone in all infants included in the RCTs, intravenous immunoglobulin plus phototherapy significantly reduced the use of exchange transfusion, the number of transfusions per child, the maximum serum bilirubin levels, the duration of phototherapy, and the duration of hospital stay (use of exchange transfusion: 3 RCTs; 14/96 [15%] with intravenous immunoglobulin plus phototherapy v 48/93 [52%] with phototherapy; RR 0.28, 95% CI 0.17 to 0.47; $P < 0.00001$; number of transfusions per child: 3 RCTs, 189 infants; WMD -0.52 , 95% CI -0.70 to -0.35 ; $P < 0.0001$; maximum serum bilirubin levels: 3 RCTs, 189 infants; WMD -46.55 micromol/L, 95% CI -68.39 micromol/L to -24.71 micromol/L; $P = 0.00003$; duration of phototherapy: 1 RCT, 116 infants; WMD -22.37 hours, 95% CI -34.83 hours to -9.91 hours; $P = 0.000044$; duration of hospital stay: 1 RCT, 116 infants; WMD -23.48 hours, 95% CI -37.71 hours to -9.25 hours; $P = 0.0012$).^[44]

The review found that compared with phototherapy alone, intravenous immunoglobulin plus phototherapy prophylaxis (defined as use in infants with evidence of isoimmune haemolysis within the first few hours of life, before bilirubin has been shown to rise) significantly reduced the use of exchange transfusion and the number of transfusions per child (exchange transfusion: 2 RCTs; 6/38 [16%] with intravenous immunoglobulin plus phototherapy v 26/35 [74%] with phototherapy; RR 0.21, 95% CI 0.10 to 0.45; $P = 0.00006$; number of transfusions per child: 2 RCTs, 73 infants; WMD -0.89 , 95% CI -1.18 to -0.60 ; $P < 0.00001$). However, the review found no significant difference between groups in maximum serum bilirubin levels (2 RCTs, 73 infants; WMD -3.83 micromol/L, 95% CI -46.01 micromol/L to $+38.35$ micromol/L; $P = 0.86$).^[44]

The review found that in infants with Rh incompatibility only, intravenous immunoglobulin plus phototherapy significantly reduced the use of exchange transfusion (3 RCTs; 8/51 [16%] with intravenous immunoglobulin plus phototherapy v 31/45 [69%] with phototherapy; RR 0.23, 95% CI 0.12 to 0.44; $P = 0.000014$) and significantly reduced the number of exchange transfusions per child (3 RCTs, 96 infants; WMD -0.90 , 95% CI -1.17 to -0.63 ; $P < 0.0001$) compared with intravenous immunoglobulin alone. However, the review found no significant difference between groups for infants with Rh incompatibility only, in maximum serum bilirubin levels, duration of phototherapy, or duration of hospital stay (serum bilirubin levels: 3 RCTs, 96 infants; WMD -25.98 micromol/L, 95% CI -58.69 micromol/L to $+6.75$ micromol/L; $P = 0.12$; duration of phototherapy: 1 RCT, 23 infants; WMD -10.32 hours, 95% CI -37.78 hours to $+17.14$ hours; $P = 0.46$; duration of hospital stay: 1 RCT, 23 infants; WMD -20.22 hours, 95% CI -48.17 hours to $+7.73$ hours; $P = 0.16$).^[44]

The review found that in infants with ABO incompatibility only, compared with phototherapy alone, intravenous immunoglobulin plus phototherapy significantly reduced use of exchange transfusion, maximum serum bilirubin levels, duration of phototherapy, and duration of hospital stay (use of exchange transfusion: 1 RCT; 6/45 [13%] with intravenous immunoglobulin plus phototherapy v 17/48 [35%] with phototherapy; maximum serum bilirubin levels: 1 RCT, 93 infants; WMD -60.58 micromol/L, 95% CI -83.21 micromol/L to -37.95 micromol/L; $P < 0.00001$; duration of phototherapy: 1 RCT, 93 infants; WMD -22.84 hours, 95% CI -37.99 hours to -7.69 hours; $P = 0.0031$; duration of hospital stay: 1 RCT, 93 infants; WMD -31.51 hours, 95% CI -49.30 hours to -13.72 hours; $P = 0.00052$). However, the review found no significant difference between groups in the number of exchange transfusions per child (1 RCT, 93 infants; WMD -0.17 , 95% CI -0.37 to $+0.03$; $P = 0.09$).^[44]

The review found that in infants with established jaundice only, compared with phototherapy alone, intravenous immunoglobulin plus phototherapy significantly reduced use of exchange transfusion, number of exchange transfusions per child, maximum serum bilirubin levels, duration of phototherapy, and duration of hospital stay (use of exchange transfusion: 1 RCT; 8/58 [14%] with intravenous immunoglobulin plus phototherapy v 22/58 [38%] with phototherapy; RR 0.36, 95% CI 0.18 to 0.75; $P = 0.0061$; number of exchange transfusions per child: 1 RCT, 116 infants; WMD -0.31 , 95% CI -0.53 to -0.09 ; $P = 0.0055$; maximum serum bilirubin levels: 1 RCT, 116 infants; WMD

–62.20 micromol/L, 95% CI –87.73 micromol/L to –36.67 micromol/L; $P < 0.0001$; duration of phototherapy; 1 RCT, 116 infants; WMD –22.37 hours, –34.83 hours to –9.91 hours; $P = 0.00044$; duration of hospital stay: 1 RCT, 116 infants; WMD –23.48 hours, 95% CI –37.71 hours to –9.25 hours; $P = 0.0012$).^[44]

The first subsequent RCT (112 healthy term infants, with ABO haemolytic disease and positive direct Coombs' test) compared intravenous immunoglobulin plus phototherapy versus phototherapy alone.^[45] The RCT found that compared with phototherapy alone, intravenous immunoglobulin plus phototherapy significantly reduced the need for exchange transfusion and mean duration of phototherapy (need for exchange transfusion: 4/56 [7%] with intravenous immunoglobulin *v* 16/56 [29%] with phototherapy; $P = 0.007$; mean duration of phototherapy: 3.84 days with intravenous immunoglobulin *v* 4.40 days with phototherapy; $P = 0.036$). However, the RCT found no significant difference between groups in the mean length of hospital stay (7.05 days with intravenous immunoglobulin *v* 7.46 days with phototherapy; $P = 0.63$).^[45]

The second subsequent RCT (34 infants, gestational age at least 37 weeks, positive direct Coombs' test, ABO incompatibility, serum bilirubin rising to 5 mg/dL/hour or greater, serum bilirubin less than threshold for exchange transfusion on admission, no risk factors for sepsis, no glucose-6-phosphate dehydrogenase) compared intravenous immunoglobulin plus phototherapy (every 12 hours for 3 doses) versus phototherapy alone.^[46] The RCT found that compared with phototherapy alone, intravenous immunoglobulin plus phototherapy significantly reduced the number of infants requiring exchange transfusion, mean number of exchange transfusions required per infant, duration of phototherapy, and length of hospital stay (number of infants requiring exchange transfusion: 3/17 [18%] with intravenous immunoglobulin *v* 11/17 [65%] with phototherapy; $P = 0.005$; mean number of exchange transfusions required per infant: 0.17 ± 0.39 with intravenous immunoglobulin *v* 1.11 ± 0.99 with phototherapy; $P = 0.001$; duration of phototherapy: 4.94 ± 0.96 days with intravenous immunoglobulin *v* 6.41 ± 2.00 days with phototherapy; $P = 0.01$; length of hospital stay: 6 ± 1.00 days with intravenous immunoglobulin *v* 7.41 ± 2.09 days with phototherapy; $P = 0.01$).^[46]

Harms:

Immunoglobulin versus no treatment:

The RCT reported that no adverse effects of intravenous immunoglobulin were observed.^[42]

Immunoglobulin versus phototherapy:

The RCT reported that no adverse effects (including heart rate increase, tachypnoea, fever, dysphoria, or face flushing) were observed in either group.^[43]

Immunoglobulin plus phototherapy versus phototherapy alone:

The review reported no significant difference between groups in adverse effects (3 RCTs; 0/96 [0%] with intravenous immunoglobulin plus phototherapy *v* 3/93 [3%] with phototherapy alone; RR 0.25, 95% CI 0.03 to 2.17; $P = 0.21$); however, the review stated that none of these reactions were a consequence of intravenous immunoglobulin treatment.^[44] The adverse effects in the control group included hypoglycaemia, hypocalcaemia, and sepsis.^[44]

The first and second subsequent RCTs reported no immediate adverse effects related to intravenous immunoglobulin, including fever, allergic reactions, volume overload, or haemolysis.^{[45] [46]}

Comment:

None of the studies included in the systematic review were of high quality.^[44] However, it seems that intravenous immunoglobulin given to high-risk infants is effective at reducing the need for exchange transfusion and the total number of exchange transfusions required. There is no evidence to suggest that it prevents mortality or neurodevelopmental sequelae. Intravenous immunoglobulin seems safe and well tolerated; however, supplies are limited. Rare complications of intravenous immunoglobulin administration include haemolysis, renal failure, and sepsis.^[44] More research is required into the long-term effects of intravenous immunoglobulin treatment, which patients are most likely to benefit, and dosing and timing of administration.

Clinical guide:

Administration of intravenous immunoglobulin in infants with haemolytic hyperbilirubinaemia reduces the need for exchange transfusion.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Immunoglobulin New option added with one systematic review^[44] and 4 RCTs.^{[42] [43] [45] [46]} Categorised as beneficial.

Exchange transfusion New evidence added.^[36] Categorisation unchanged (Likely to be beneficial by consensus) because new evidence comparing single volume exchange transfusion (SVET) versus double volume exchange transfusion (DVET) was insufficient to judge the effects of these interventions.

Hospital phototherapy New evidence added.^{[10] [15] [16] [17] [18] [19] [20] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [33] [32] [34]} Categorisation unchanged (Beneficial).

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Paul Woodgate

Neonatologist

Department of Neonatology

Mater Mother's Hospital

Brisbane

Australia

Luke Anthony Jardine

Neonatologist

Department of Neonatology

Mater Mothers' Hospital

Brisbane

Australia

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TABLE GRADE evaluation of interventions for neonatal jaundice

Important out-comes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evi- dence	Quality	Con- sis- tency	Direct- ness	Ef- fect size	GRADE	Comment
What are the effects of treatments for unconjugated hyperbilirubinaemia in term and preterm infants?									
1 (unclear) ^[6] ^[9]	Neurological/neurodevel- opmental	Conventional phototherapy v no treatment	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for use of low intensity photother- apy, which may have affected result
1 (417) ^[6]	Need for exchange transfusion	Conventional phototherapy v no treatment	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for use of low intensity photother- apy, which may have affected results in some subgroups
2 (542) ^[6] ^[7]	Serum bilirubin levels	Conventional phototherapy v no treatment	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for unexplained imbalance between groups in 1 RCT, which may affect interpretation of results
1 (80) ^[10]	Serum bilirubin levels	Continuous phototherapy v no treatment	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for no statistical analysis between groups
1 (80) ^[10]	Serum bilirubin levels	Intermittent phototherapy v no treatment	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for no statistical analysis between groups
1 (46) ^[11]	Duration of treatment	Fibreoptic phototherapy v no treat- ment	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events (3 in total)
1 (46) ^[11]	Serum bilirubin levels	Fibreoptic phototherapy v no treat- ment	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete re- porting of results
3 (214) ^[11]	Need for exchange transfusion	Conventional phototherapy v fibreop- tic phototherapy	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria. Directness point deducted for inconsistent interventions be- tween trials (BiliBlanket, Wallaby, conventional phototherapy)
At least 10 (at least 1005) ^[11] ^[12] ^[13]	Duration of treatment	Conventional phototherapy v fibreop- tic phototherapy	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria. Directness point deducted for inconsistent interventions be- tween trials (BiliBlanket, Wallaby, conventional phototherapy)
At least 6 (at least 412) ^[11] ^[12]	Serum bilirubin levels	Conventional phototherapy v fibreop- tic phototherapy	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria. Directness point deducted for inconsistent interventions be- tween trials (BiliBlanket, Wallaby, conventional phototherapy)
1 (42) ^[11]	Need for exchange transfusion	Double phototherapy v single pho- totherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events (2 in total) indicating weak power to demonstrate difference between groups
9 (749) ^[11] ^[13] ^[14]	Duration of treatment	Double phototherapy v single pho- totherapy	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria. Directness point deducted for inconsistent interventions be- tween trials (BiliBlanket, Wallaby, conventional phototherapy)

Important outcomes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
10 (809) ^{[11] [13] [14] [15]}	Serum bilirubin levels	Double phototherapy v single phototherapy	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of quasi-randomised trials, and variation in inclusion criteria and outcome criteria. Directness point deducted for inconsistent interventions between trials (BiliBlanket, Wallaby, conventional phototherapy)
1 (40) ^[16]	Serum bilirubin levels	Triple phototherapy v double phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
1 (34) ^[18]	Duration of treatment	Intermittent phototherapy v continuous phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for restricted population
3 (228) ^{[10] [17] [18]}	Serum bilirubin levels	Intermittent phototherapy v continuous phototherapy	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of events in some analyses (1 and 5 in two analyses) indicating weak power to demonstrate differences between groups
1 (774) ^[19]	Duration of treatment	Close phototherapy v distant light-source phototherapy	4	0	0	−1	0	Moderate	Directness point deducted for small number of comparators
1 (59) ^[20]	Duration of treatment	Increased skin exposure v standard skin exposure phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
1 (59) ^[20]	Serum bilirubin levels	Increased skin exposure v standard skin exposure phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
1 (unclear, <101) ^[21]	Serum bilirubin levels	Fluorescent lamps v halide lamps	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (72) ^[22]	Duration of treatment	Fluorescent v blue fluorescent	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for no statistical analysis between groups
1 (72) ^[22]	Serum bilirubin levels	Fluorescent v blue fluorescent	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for no statistical analysis between groups
1 (262) ^[23]	Duration of treatment	Blue fluorescent v green fluorescent	4	0	0	−1	0	Moderate	Directness point deducted for restricted population
2 (356) ^{[23] [24]}	Serum bilirubin levels	Blue fluorescent v green fluorescent	4	−1	0	−1	0	Low	Quality point deducted for subgroup analysis (no overall analysis reported) in 1 RCT. Directness point deducted for restricted population
2 (87) ^{[27] [28]}	Duration of treatment	Blue-green fluorescent v blue fluorescent	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
4 (313) ^{[25] [26] [27] [28]}	Serum bilirubin levels	Blue-green fluorescent v blue fluorescent	4	−2	−1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
3 (239) ^{[29] [27] [30]}	Duration of treatment	Blue LED v conventional quartz-halogen	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for variation in interventions (5–6 blue LED; 1–3 halogen-quartz bulbs) affecting generalisability of results

Important out-comes	Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (239) ^[29] ^[27] ^[30]	Serum bilirubin levels	Blue LED v conventional quartz-halogen	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for variation in interventions (5–6 blue LED; 1–3 halogen-quartz bulbs) affecting generalisability of results
1 (66) ^[31]	Serum bilirubin levels	Blue LED v blue fluorescent	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for small number of comparators and co-interventions
1 (79) ^[27]	Duration of treatment	Blue-green LED v conventional quartz-halogen	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (79) ^[27]	Serum bilirubin levels	Blue-green LED v conventional quartz-halogen	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (83) ^[32]	Neurological/neurodevelopmental	Prophylactic v threshold phototherapy	4	−2	0	−1	0	Very low	Quality point deducted for sparse data and no intention-to-treat analysis. Directness point deducted for composite outcome (death and cerebral palsy)
1 (unclear, <96) ^[32]	Duration of treatment	Prophylactic v threshold phototherapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (at least 92) ^[32]	Serum bilirubin levels	Prophylactic v threshold phototherapy	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (1974) ^[33]	Mortality	Low threshold v high threshold phototherapy	4	0	0	−1	0	Moderate	Directness point deducted for composite outcome
1 (1854) ^[33]	Neurological/neurodevelopmental	Low threshold v high threshold phototherapy	4	−1	0	0	0	Moderate	Quality point deducted for no intention-to-treat analysis
1 (unclear) ^[33]	Need for exchange transfusion	Low threshold v high threshold phototherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (unclear) ^[33] ^[34]	Duration of treatment	Low threshold v high threshold phototherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (unclear) ^[33]	Serum bilirubin levels	Low threshold v high threshold phototherapy	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (100) ^[35]	Duration of treatment	Compact fluorescent light phototherapy v standard length tube light phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
1 (100) ^[35]	Serum bilirubin levels	Compact fluorescent light phototherapy v standard length tube light phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of comparators
1 (20) ^[36]	Duration of treatment	Single volume exchange v double volume exchange transfusion	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for restricted population
1 (20) ^[36]	Serum bilirubin levels	Single volume exchange v double volume exchange transfusion	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for restricted population

Important outcomes		Mortality, neurological/neurodevelopmental, need for exchange transfusion, duration of treatment, serum bilirubin levels, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
5 (336) ^[41]	Neurological/neurodevelopmental delay	Tin-mesoporphyrin v standard treatment	4	−3	0	−1	0	Very low	Quality points deducted for incomplete reporting of results, non-systematic combination of data, and unclear outcome assessment. Directness point deducted for poor follow-up
At least 2 (at least 170) ^{[39] [40] [41]}	Duration of treatment	Tin-mesoporphyrin v standard treatment	4	−3	0	−1	0	Very low	Quality points deducted for incomplete reporting of results, non-systematic combination of data, and open-label study. Directness point deducted for no direct statistical comparison between groups in 1 RCT
Unclear (unclear) ^[41]	Serum bilirubin levels	Tin-mesoporphyrin v standard treatment	4	−3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, non-systematic combination of data, and selective reporting of only 1 dose
1 (40) ^[42]	Duration of treatment	Immunoglobulin v no treatment	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) ^[42]	Serum bilirubin levels	Immunoglobulin v no treatment	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (121) ^[43]	Need for exchange transfusion	Immunoglobulin v phototherapy	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for mixed control group (continuous and intermittent phototherapy)
1 (121) ^[43]	Duration of treatment	Immunoglobulin v phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for mixed control group (continuous and intermittent phototherapy)
1 (121) ^[43]	Serum bilirubin levels	Immunoglobulin v phototherapy	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for mixed control group (continuous and intermittent phototherapy)
At least 7 (at least 408) ^{[44] [45] [46]}	Need for exchange transfusion	Immunoglobulin plus phototherapy v phototherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for weak methods
At least 3 (at least 262) ^{[44] [45] [46]}	Duration of treatment	Immunoglobulin plus phototherapy v phototherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for weak methods
At least 3 (at least 189) ^[44]	Serum bilirubin levels	Immunoglobulin plus phototherapy v phototherapy alone	4	−1	0	0	0	Moderate	Quality point deducted for weak methods

Type of evidence: 4 = RCT.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.